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NEURONAL ACTIVITY RELATED TO FACES AND MATCHING IN HUMAN RIGHT NONDOMINANT TEMPORAL CORTEX

by JEFFREY G. OJEMANN, GEORGE A. OJEMANN *and* ETTORE LETTICH

(From the Department of Neurological Surgery, University of Washington, Seattle, Washington, USA)

SUMMARY

Neuronal activity was recorded from 13 sites in right nondominant superior and middle temporal gyrus during matching of faces (FM), matching of complex figures (CM), labelling of facial emotional expression (FE) and object naming (N) in 11 patients undergoing craniotomy under local anaesthesia. These extracellular recordings were divided into 21 neuronal populations of one to a few cells, using amplitude window discriminators. Sixty-two percent of those populations showed statistically significant changes in activity during FM; 52% during FE; 38% during N and 38% during CM. Fifty-one percent of changes were in the first 1.3 s of each task and 33% in the next 1.3 s, when overt speech responses to the tasks occurred. Significant changes lasting throughout the 4 s allotted to each task were not seen. Functional correlates of some populations were derived from patterns of changes during FM and other tasks: four populations were related to 'matching', in that significant changes occurred with FM and CM. One of these populations, and six other populations were related to face perception, with significant change with FM and FE, confirming the presence in man of neuronal activity related to faces, as previously described from primate cortex. Six populations increased activity with overt speech; four of these showed greater increases when overt speech was in response to a visuospatial task compared with the lexical task.

INTRODUCTION

Changes in neuronal activity in response to faces have been extensively described in recording from monkey cortex (Perrett *et al.*, 1984; Rolls, 1984). However, the presence of such activity in humans has not been established. Craniotomies under local anaesthesia, usually for medically intractable epilepsy, provide an opportunity to record neuronal activity in human cortex during measures of various higher functions. Most often, this clinical opportunity provides access to anterior temporal cortex. This opportunity has been previously utilized by us to investigate cortical neuronal changes during several language functions and recent verbal memory (Ojemann *et al.*, 1988; Creutzfeldt and Ojemann, 1989; Creutzfeldt *et al.*, 1989*a*,*b*). Several lines of evidence, especially studies using rapid visual half-field presentation, suggest that human right, nondominant hemisphere is particularly important in the processing of faces (Rizzolatti *et al.*, 1971; Hilliard, 1973; Klein *et al.*, 1976; Sackeim *et al.*, 1978). Thus the present study was undertaken, recording neuronal activity intraoperatively from the right anterior temporal lobe in response to two measures related to faces: a direct match of faces and labelling of depicted facial emotional expressions. Activity was also recorded during another

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measure related to nondominant hemisphere function, matching of complex figures and a language task related to the dominant hemisphere, object naming. The findings reported here have been previously published in abstract form (Ojemann *et al.*, 1989).

METHODS

Subjects

Eleven adults undergoing right anterior temporal lobectomies under local anaesthesia for the treatment of medically intractable epilepsy were the subjects for this study. All patients were known to be left brain dominant for language, based on pre-operative intracarotid amobarbital perfusion assessment (Wada and Rasmussen, 1960). Mean age was 32.6 yrs, range 18–55. Mean pre-operative performance IQ was 85.5, range 74–102. All patients were on therapeutic levels of antiepileptic drugs, most often carbamazepine, and received Decadron, 4 mg every 6 h. Seizure onsets occurred at a mean age of 15 yrs (range 3 mths to 52 yrs). An etiology for the seizures other than mesial temporal sclerosis was present in three cases: a low-grade astrocytoma, a cavernous angioma and chronic temporal lobe contusion from the condyle of the mandible due to a bony defect in the middle fossa (reported in Clarke *et al.*, 1988).

Craniotomy was conducted under a local anaesthetic field block with 0.5% lidocaine and 0.25% bupivacaine, placed 2 h or more before microelectrode recording. Most patients received fentanyl, 50 μg, and droperidol, 2.5 mg, intravenously shortly before placement of the block. No additional medications were given before microelectrode recording, which preceded any resection. Medications, the extent of the craniotomy and subsequent resection and use of local anaesthesia were all determined by clinical considerations. Patients gave specific informed consent for the microelectrode research study, following prior approval of that study by the University of Washington Institutional Review Board.

Recording

Due to the invasive nature of microelectrode recording, it was restricted to cortex that was to be subsequently resected. This limited recording sites to anterior portions of superior and middle temporal gyri. Sites were selected near the posterior margin of the planned resection, in the portion of the resection with the least epileptic activity on electrocorticography.

Microelectrodes were fashioned from tungsten wire, coated with epoxylite and tips electrolytically sharpened to 1–5 μm diameter. Electrode impedances were 3–7 MΩ. Electrodes were mounted in a Trent-Wells hydraulic drive, after backloading through a hole in a 1.5 cm diameter plexiglas footplate. Electrodes and the microdrive were separately sterilized immediately prior to use. The microdrive was positioned perpendicular to the cortical surface, the footplate exerting gentle pressure, but not blanching pial vessels. The microelectrode was then advanced until neuronal activity was recorded that was free of injury discharge, or epileptic bursts (Calvin *et al.*, 1973). Successful recordings were obtained from two side by side microelectrodes in one patient.

Tasks

Once stable recordings were obtained, the patient performed eight or more trials of the main test measuring matching of faces and complex figures, labelling of facial emotional expressions and object naming. This test was presented by slides, one every 4 s. Figure 1 depicts the content of the four slides that made up one trial of that task. The first slide of each trial was the measure of face matching (FM). The patient matched the face above the line to one of the three below, arranged vertically, indicating aloud his selection with the appropriate letter. The second slide was a measure of labelling facial emotional expression (FE). That slide showed standardized photographs of actors' faces depicting one of seven standard emotions, adapted from Ekman and Friesen (1976). The patient stated aloud the emotion depicted. The third slide of each trial was a line-drawing picture of a common object. The patient stated aloud the name. The fourth slide depicted a complex figure above a line, and three similar figures arranged horizontally below, labelled with letters. The patient stated aloud the letter of the figure below matching the one above. Figures were derived from Vanderplas and Garvin (1959), as those with relatively few verbal associations. Patients were trained in this test the night before operation.

In addition, an auditory language task was administered to 10 subjects. This task, previously described (Creutzfeldt *et al.*, 1989*a*), was a tape-recorded list of common words, each preceded by a 1000 Hz tone.

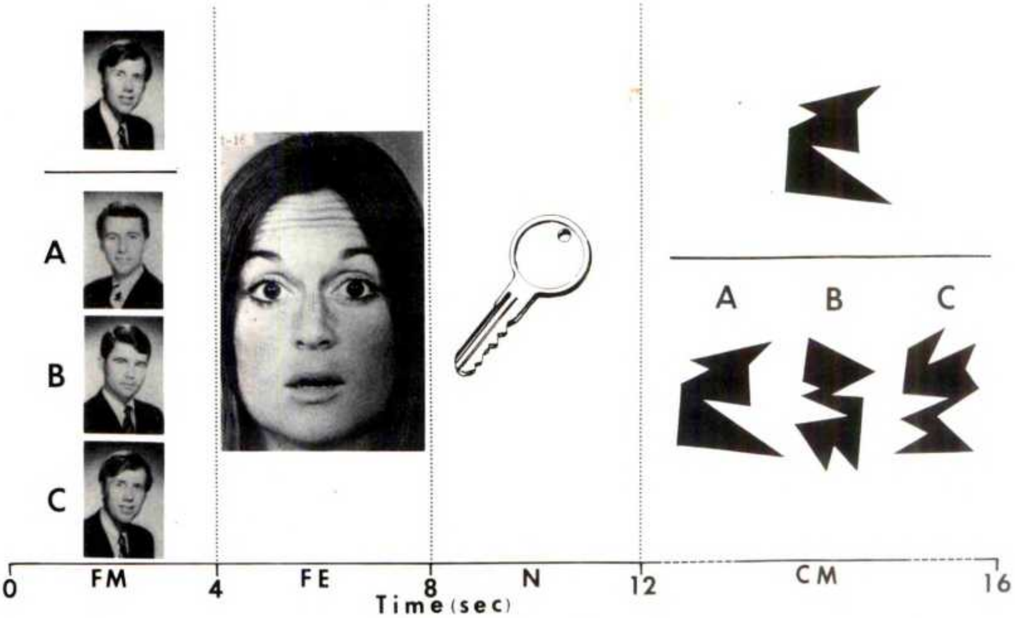

FIG. 1. One trial of the main test administered during microelectrode recording. Each trial consists of four slides, each shown for 4 s. FM = face matching; FE = labelling of facial emotional expression; N = object naming; CM = complex figure matching. See text for required patient responses to each slide. Eight trials of this test were administered to each patient.

The list was administered twice, once with the instruction to listen to it, and the second time with the instruction to repeat each word aloud. Words were presented at an interval of 5 s.

Analysis

Activity from microelectrodes, markers indicating when slides changed, and patients' responses were tape recorded on a system with a frequency response of 100 Hz to 6.5 kHz for later analysis. Action potentials on microelectrode recordings were converted into pulses with a Bak window discriminator, and counted with a PDP 11/23 computer. When a microelectrode recording demonstrated action potentials of different amplitudes, the window discriminator was set at a high threshold, to obtain a population containing only the largest action potentials probably from a single neuron, and also at a low threshold, yielding a population of only small action potentials, probably representing activity of one or more neurons and different from those generating the high threshold action potentials.

Activity during each slide was then divided into three equal epochs, each 1.3 s long. Overt speech responses generally occurred in the second of these epochs. Thus the approximate behavioural correlates of the epochs are: first epoch, perception and processing; second epoch, overt response; third epoch, pause between tasks.

For statistical analysis, activity in each epoch of one trial of the main test was ranked, and compared with the mean rank of the 12 epochs in each trial. For each epoch, that difference for all trials was analysed with the Wilcoxon matched-pairs signed rank test (Siegel, 1956). As there were no predictions of direction of changes, a two-tailed probability of less than 0.05 was considered significant.

RESULTS

Recordings were obtained from 21 neuronal populations at 13 recording sites in the 11 patients. Figure 2 is a typical recording. Fifteen of these populations from 11 patients

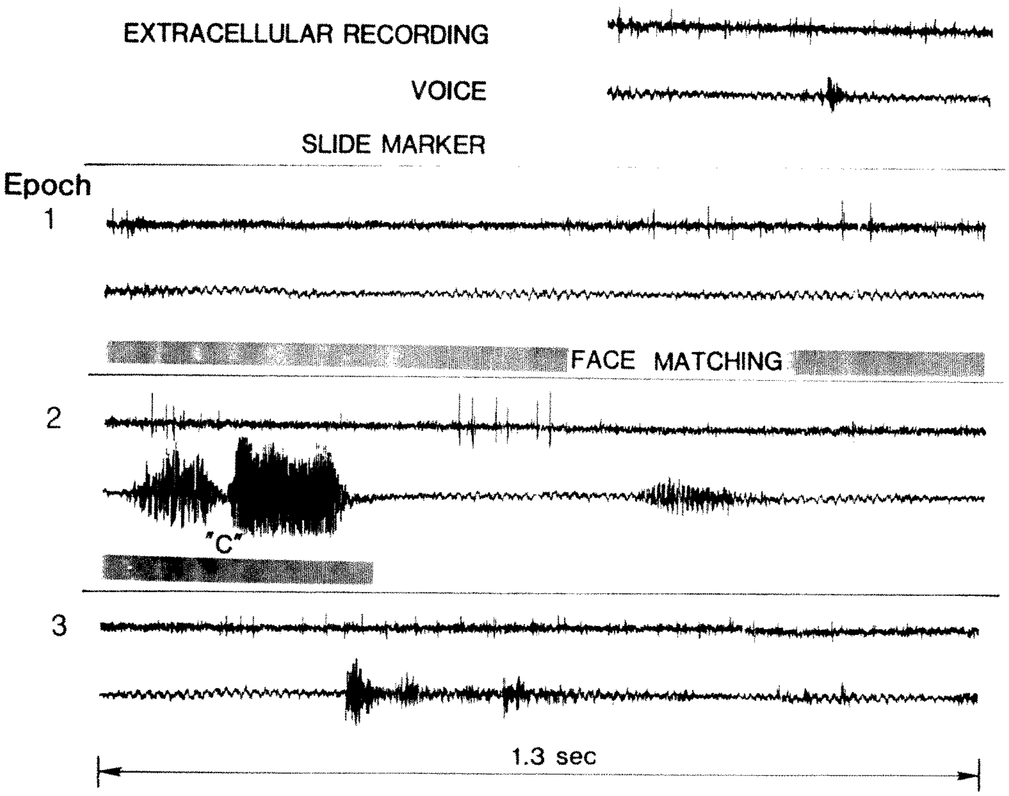

FIG. 2. Typical extracellular microelectrode recording during a face-matching slide (FM). Recording is continuous, from 0.5 s before presentation of face-matching slide, to presentation of next slide of main test. Voice channel records patient's responses.

contained action potentials of relatively high uniform amplitude, most likely reflecting activity of a single neuron. Mean peak activity during any epoch of the behavioural measures in those populations was 27 discharges per second (range 11–91/s). The remaining six neuronal populations included only low amplitude action potentials, often with somewhat higher peak levels of activity. Those populations are more likely to reflect activity of more than one neuron. The major behavioural relationships described below were identified in high amplitude—probably single neuron—populations, as well as low amplitude populations.

Statistically significant changes in the frequency of activity recorded during some epoch of the main test were identified in 17 neuronal populations, at least one in each subject. The Table indicates significant increases or decreases in activity in each epoch of the four tasks that make up the main test: matching of faces (FM), labelling of facial emotional expressions (FE), object naming (N) and complex figure matching (CM). As is apparent from the Table, 51% of all significant changes occurred in first epochs, 33% in second epochs and 16% in third. For any one population, changes were present in from one to six epochs. However, no population showed significant changes in all three epochs of any one task.

TABLE CHANGES IN NEURONAL ACTIVITY WITH TASKS*

				Task.	*FM*			*FE*			*N*			*CM*			
Patient	*Site***	*Electrodes***	*Populations****	*Epoch.*	*I*	*II*	*III*	*I*	*II*	*III*	*I*	*II*	*III*	*I*	*II*	*III*	*Speech*
8717	1	A			−	+					−			−	+		+
		B															
	2	A	1		−		+							−	+		+
			2					−				+					+
		B												+			
8710			2														
			1			+								−			
8738					−			−			+			+			
8628	1				+	+			+								
	2		1		−			−									
			2								+						
8613			1														
			2		+	−							−				
8816			1														
			2			+		+		−							
8736			1						+		+			−		−	+
			2		−				+	+			−	−			+
8730							−	+									
8424					+	+			+			+		+	+		+
8508						+		+									
8511							−		−								
Excitation					3	6	1	3	4	1	3	2	0	3	3	0	
Inhibition					5	1	2	3	1	1	1	0	2	5	0	1	
Total					8	7	3	6	5	2	4	2	2	8	3	1	

*All changes significant at $P < 0.05$ (two-tailed) Wilcoxon signed rank test. **Two recording sites, the second 1 mm deeper in cases 8717, 8628. Two adjacent microelectrodes, A and B in case 8717. ***For those recordings when nearly neuronal populations recorded by a single microelectrode were separated by window discriminator. + indicates significant increase, − indicates significant decrease in activity during specific task epoch. Tasks and epochs defined in text.

Significant changes during some epoch of the face-matching task were evident in 13 populations from 11 patients, 62% of the total population. Changes during some epoch of facial expression labelling were present in 11 populations from nine patients (52% of populations), for naming, eight populations in six patients (38%) and complex figure matching, eight populations in five patients (38%). Changes during FE or N were predominantly excitatory (Table). FM and CM showed an overall pattern of reduced activity in first epochs, and excitatory in second epochs, although a given population rarely showed both effects.

In some populations, changes were confined to a single task. Four populations (in four patients) had significant changes only in a first or second epoch of a single task, one population during each task. Figure 3 illustrates the population with first or second

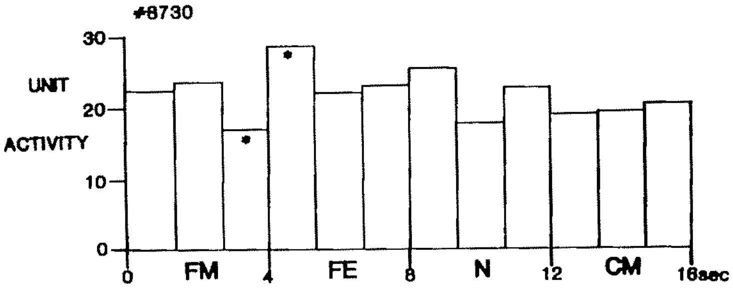

FIG 3 Neuronal activity increasing in first epoch of labelling of facial emotional expressions (FE) and decreasing in third epoch of face matching (FM) Each bar is average activity in each 1 3 s epoch for all eight trials of the main test * = changes significant at $P < 0\ 05$. This recording contained only activity of uniform amplitude, from mid portion of right middle temporal gyrus at depth of 6 mm in case 8730, a 25-yr-old female

epoch changes only in FE. Three populations in three patients had significant changes in first or second epochs of all four tasks (Fig. 4), although significant changes were in the same direction in all tasks in only one case, increases in all second epochs in a population related to overt speech.

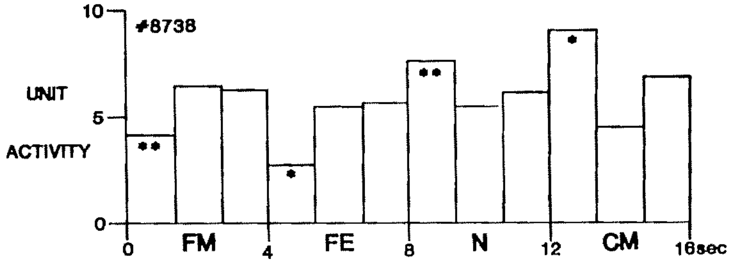

FIG 4 Neuronal activity decreasing with face perception [first epochs of face-matching (FM) and labelling expressions (FE)], and increasing during first epochs of object naming (N) and complex figure matching (CM). Presentation is as in Fig. 3 * = $P < 0.05$ ** = $P < 0.01$ This recording contained only activity of uniform amplitude, from right superior temporal gyrus at depth of 2 mm, in case 8738, a 55-yr-old female

Ten populations (in eight patients) showed changes in the same direction (excitation or inhibition) in particular combinations of FM and other tasks, often in the same epoch. Four populations (in three patients) showed changes in the same direction in both FM and CM, 75% in the same epochs. Figure 5 illustrates one of these populations. One of these populations, and six other populations (in five patients) showed changes in the same direction during both FM and FE, though in only two populations were changes all in the same epochs. Figures 4 and 6 illustrate two of these populations with changes in both FM and FE, one with increased activity, the other decreased activity.

Six populations, in four patients, showed both increased activity in one or more second

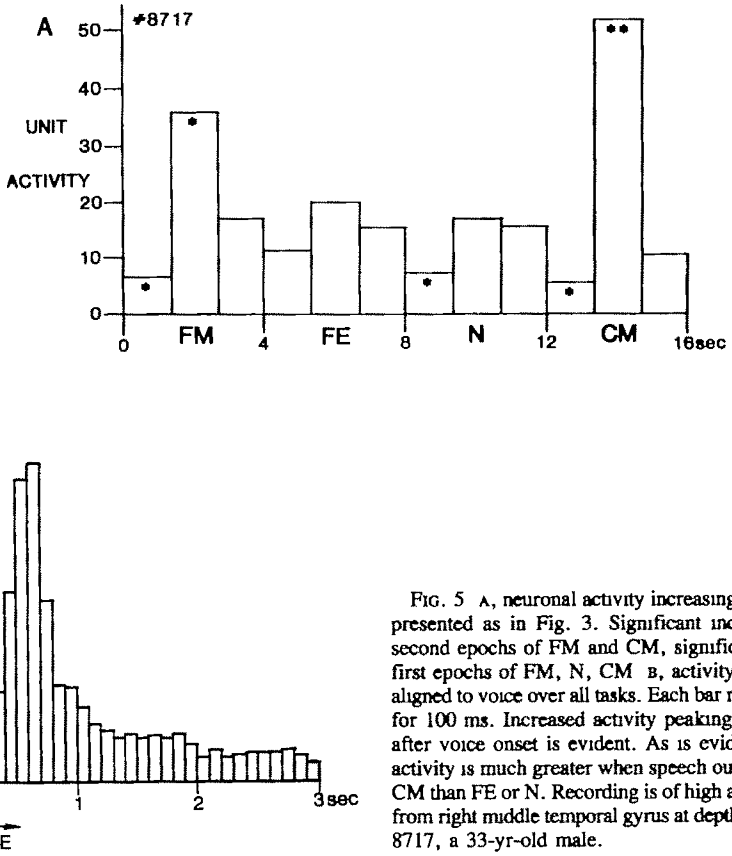

FIG. 5 A, neuronal activity increasing with 'matching' presented as in Fig. 3. Significant increases occur on second epochs of FM and CM, significant decreases in first epochs of FM, N, CM B, activity of same neuron aligned to voice over all tasks. Each bar represents activity for 100 ms. Increased activity peaking at 600–700 ms after voice onset is evident. As is evident from A, this activity is much greater when speech output is for FM or CM than FE or N. Recording is of high amplitude activity from right middle temporal gyrus at depth of 6 mm in case 8717, a 33-yr-old male.

epochs (the epoch containing speech output) of the main behavioural test, and also during overt speech on the auditory repetition test (Table). Figures 5 and 7 illustrate activity of two such populations during both tests. As is evident in the 'A' part of those figures, the magnitude of this increased activity is much greater when associated with the speech output from visuospatial tasks than from a language task. In the case illustrated in Fig. 5, activity is maximal when speech output was from FM and CM. In the other case (Fig. 7), maximal increased activity occurred during speech output as part of FE. Similar findings were evident in two of the four other populations showing increased activity with speech output.

Sites of microelectrode recording are illustrated in Fig. 8. Changes related only to labelling of facial emotional expressions were confined to middle temporal gyrus. All populations showing changes with overt speech that were of greater magnitude when the speech represented output from visuospatial rather than language tasks were also confined to middle temporal gyrus. Changes in activity related to FM alone or when combined with CM or FE were recorded widely.

Recording depths varied from 1 to 10 mm (mean 5 mm). No relation between behavioural changes and recording depths was established. In two patients, recordings were obtained at two different depths (1 mm apart) with separate behavioural assessments.

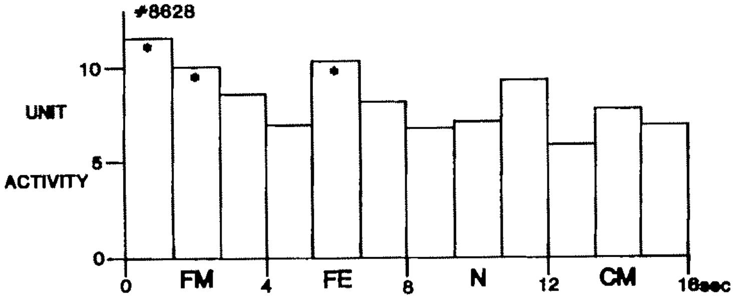

FIG. 6. Neuronal activity related to face perception Significant increases occur in first and second epochs of FM, and second epoch of FE Recording presented as in Fig 3; it contained only uniform activity, from right middle temporal gyrus at depth of 3 mm, in case 8628, a 34-yr-old male.

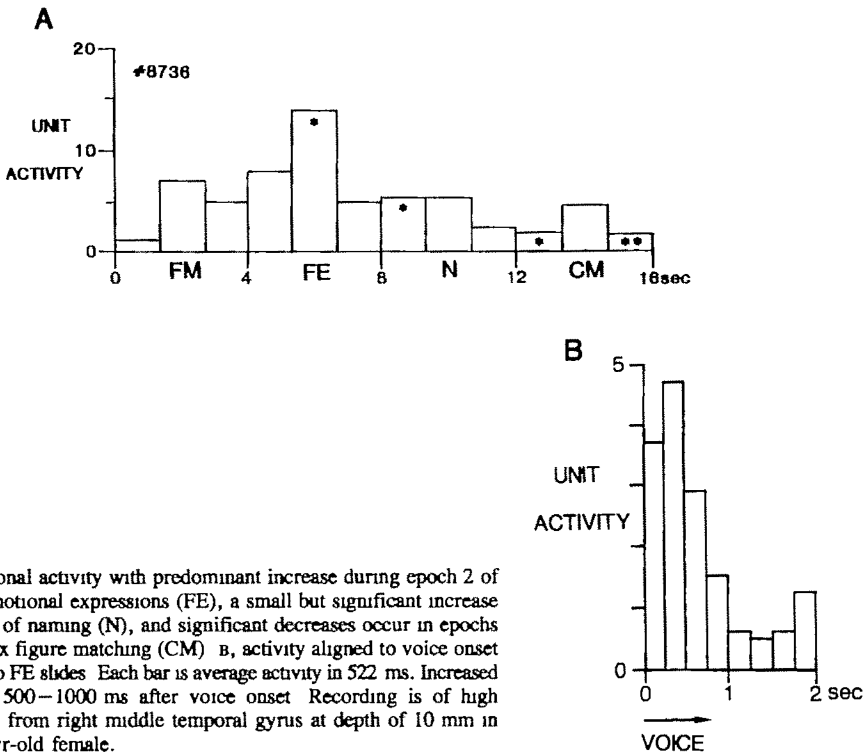

FIG. 7 A, neuronal activity with predominant increase during epoch 2 of labelling facial emotional expressions (FE), a small but significant increase occurs in epoch 1 of naming (N), and significant decreases occur in epochs 1 and 3 of complex figure matching (CM) B, activity aligned to voice onset when responding to FE slides Each bar is average activity in 522 ms. Increased activity peaks at 500–1000 ms after voice onset Recording is of high amplitude activity from right middle temporal gyrus at depth of 10 mm in case 8736, a 22-yr-old female.

In one patient, patterns of activity at the two depths were somewhat similar but activity of different neuronal populations within each level differed. In that patient, at each depth, there was one neuronal population increasing activity with FM and CM. Activity of a second population at 6 mm depth was not related to any behaviour; while 1 mm deeper a second population significantly increased activity with N, and decreased with FE while a third population was related only to CM. In the other patient, activity at 4 mm depth

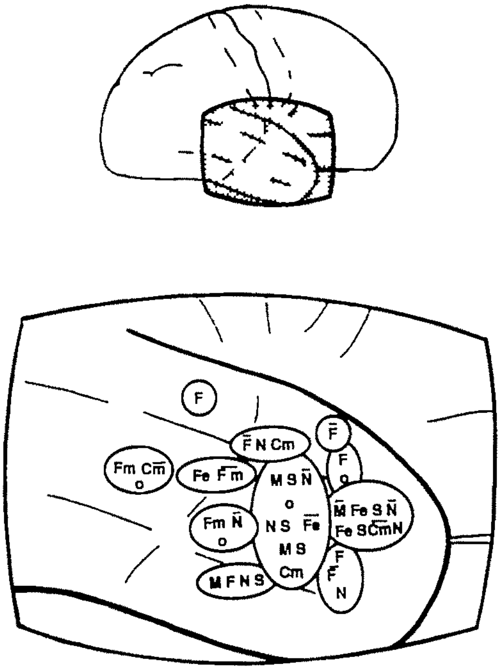

FIG 8. Location of recording sites in this study. Each circle is one recording site, for one patient Each line represents activity of one neuronal population. Significant changes in activity indicated by symbols Fm = face matching; Cm = complex figure matching; N = naming, Fe = facial expression labelling; F = Fm and Fe, M = Fm and Cm. Bar over letter signifies reduction in activity, other changes increase O = no changes S = significant increase in activity when aligned to voice onset

increased with FM and FE; at 5 mm depth one neuronal population significantly decreased with FM and FE, another increased with N. At six sites (in six patients) activity at the same depth recorded from a single microelectrode could be separated by the window discriminator into two neuronal populations (Table). At five of these sites these neurons had completely different behavioural correlates, while the two populations at the other site had similar changes to FE and CM but different activity during FM and N.

DISCUSSION

Before discussing the contribution of these findings to an understanding of the organization of right, nondominant temporal cortex, the reliability of the findings requires evaluation. This study and other studies that use statistical methodology to determine the results run some risk of reporting events that occurred by chance. That risk increases proportionately with the number of tests at a fixed level of significance (0.05, two-tailed in this study). However, there is considerable evidence that the findings reported here are *not* random events. The total number of significant events is larger than would be expected by chance. In the 252 statistical tests included here, 13 chance events would be expected, but 51 significant events were observed (Table). There is less than a one in 10 000 binomial probability of seeing that many or more events on a random basis. Furthermore, the observed events are related to specific behavioural conditions. Significant events were observed much more often during epochs 1 and 2 than expected on a chance basis (observed 43, expect eight in 168 tests, binomial $P < 0.00005$). These are the epochs involving presentation and response to stimuli. Significant events were not observed more frequently than expected on a chance basis in epoch 3, the pause between behaviours (observed eight, expected four in 84 events, binomial $P = 0.07$). Significant events in epochs 1 and 2 were observed much more often than expected on a random basis during each behaviour considered separately: face matching (observed 15, expected two in 42 tests, binomial $P < 0.0001$), face expression (observed 11, expected two in 42 tests, binomial $P < 0.0001$), complex figure matching (observed 11, expected two in 42 tests, binomial $P < 0.0001$) and even naming (observed six, expected two in 42 tests, binomial $P = 0.0174$). Moreover, the recordings reported here are a very small random sample of one to a few neurons from the very large number of neurons in each patient's temporal lobe. The probability of seeing the same patterns of charges in more than one neuron on a random basis is extremely small. Thus the presence of several neurons with the same pattern indicates that this is a feature of a large number of temporal neurons.

The non-random relative changes in neuronal activity obtained in this study were viewed in two ways. First, activity in the three different epochs of all tasks was compared. Eighty-four percent of the significant changes occurred in the first or second epochs. Thus most of the changes reported here are temporally related to the task behaviours. Secondly, relative changes between tasks were determined. Notably, nearly two-thirds of the populations changed activity with the face-matching task. Changes also present in the same population during other tasks indicate that these populations with FM changes represent two groups, one with similar changes during CM, the other similar changes with FE. The common behaviour to the FM and FE tasks that is not required in the other tasks is perception of faces. Thus seven neuronal populations related to face perception were identified. In addition, three other populations, only in middle temporal gyrus, increased activity with labelling of the emotional expression of a face.

The presence of human anterior temporal lobe neurons changing activity with faces is similar to findings in primate temporal lobe, where such neurons have also been frequently encountered (Perrett *et al.*, 1984; Rolls, 1984). However, unlike the neurons described here, activity in the monkey often dramatically increased in response to facial expressions. The human neurons described here generally had more subtle, though consistent, changes in activity in response to faces. Thus it may be that neurons more analogous to the face neurons found in monkey are present elsewhere in human cortex. Alternatively it may be that human association cortex responds to specific stimuli with less dramatic changes in activity than is seen in primates. Our study was not designed to determine if changes in activity with faces were specific to particular faces or parts or class of faces, as is the case in some primate recordings. However, the identification of human neurons related only to labelling of facial emotional expressions suggests some specificity of neuronal responses to faces in human cortex. Hasselmo *et al.* (1989) found neurons selectively responsive to facial expressions in the posterior superior temporal sulcus of the monkey.

In the subjects of this study, the resection of the recording sites and surrounding nondominant temporal lobe was not associated with any clinically detectable changes in face perception. However, the case of Rapcsak *et al.* (1989), a left-handed subject, had selective impairment in naming and pointing to emotional facial expressions following a right temporal lobe lesion. Loss of anterior temporal neurons such as those identified in the present study as related to labelling of facial emotional expressions (Fig. 7) could account for the deficits in this case. Moreover, the sites of neuronal activity related only to labelling of face expressions, and sites where electrical stimulation altered this function (Fried *et al.*, 1982) are both *only* in middle temporal gyrus. Thus for labelling of facial expressions, a consistent picture exists among neuronal recordings, stimulation mapping and at least one lesion case, all suggesting the localization of labelling of facial expressions to the middle temporal gyrus. The present study sampled only nondominant hemisphere neuronal activity and thus does not address the issue of lateralization of face perception mechanisms. However, a special role for human nondominant hemisphere in the perception of faces, and labelling of facial emotional expression has been suggested by lateralized effects with rapid simultaneous visual half-field presentation (Rizzolatti *et al.*, 1971; Hilliard, 1973; Klein *et al.*, 1976; Sackeim *et al.*, 1978) and deficits after anterior temporal resections (Milner, 1968).

Four neuronal populations with changes during face matching showed similar changes with CM. A number of behaviours are common to FM and CM and not the other tasks. Attention and perception *per se* would seem to be similar in all tasks, but FM and CM have in common perception in a linear format (vertical for faces, horizontal for complex figures), the act of matching and similar simple speech outputs ('reading the appropriate letter') that differ from the more complex word retrieval and expression of the speech outputs for N and FE. These neurons, then, seem to be related to some aspect of the 'matching' task rather than a particular category of figures (such as faces). Direct matching tasks similar to the ones in this study were disturbed after lesions in posterior parietal cortex (Heir *et al.*, 1983), while disruption of matching with nondominant cortical stimulation occurred at posterior temporal and parietal sites (Fried *et al.*, 1982) rather than the anterior temporal sites where these neurons were recorded. Thus there is some separation between the cortical areas essential for simple matching and the sites where 'matching' neurons were recorded. However, the presence of deficits in face recognition after right anterior temporal resection (Milner, 1968), and blood-flow changes there when attending to changes in shape (Corbetta *et al.*, 1990) suggest a role for these neurons in more complicated spatial analyses.

Neuronal activity related to either language perception or production in auditory tasks has been previously reported from nondominant temporal lobe (Creutzfeldt *et al.*, 1989*a*,*b*). The presence of a few neuronal populations changing activity with object naming in the present study extends this finding of language related activity in the *non*-language dominant hemisphere to visual language tasks, further evidence for neurons changing activity to a particular language task at sites well away from areas essential for that task (Ojemann, 1990). In several of the nondominant temporal neurons of this study which increased their activity with speech, that increase was much greater for specific visuospatial tasks, than for a lexical task, suggesting that these neurons provide a link between the specific visuospatial and language output. The neurons responding with speech related to facial expression seem to be the appropriate cellular substrate for the deficit in naming facial expressions in the case of Rapcsak *et al.* (1989).

The close temporal relation between changes in neuronal activity and different epochs of a task identified in the present study contrasts with the pattern of neuronal activity most often recorded during language and verbal memory tasks in dominant hemisphere (Ojemann *et al.*, 1988, 1990). The most common dominant hemisphere change has been a sustained shift in the level of activity, lasting well beyond the actual overt speech response, often for some seconds. That would appear in the present study as changes in activity in the same direction in all three epochs of a task, a pattern that was not encountered. This could be a consequence of the different tasks and formats used in studies in right or left hemisphere. However, it may also indicate that somewhat different physiological mechanisms are present in language and non-language areas. The more classical brief temporally related changes may be a characteristic of the right hemisphere, and sustained changes, perhaps reflecting selective attention, characteristic of the left hemisphere, an hypothesis requiring further investigation using similar test formats during recordings in the two hemispheres.

This study, along with other investigations of neuronal activity in human association cortex (Ojemann *et al.*, 1988; Bechtereva *et al.*, 1989; Creutzfeldt and Ojemann, 1989; Creutzfeldt *et al.*, 1989*a*,*b*; Heit *et al.*, 1989) have shown several unexpected findings. One is the ease with which a given task can apparently elicit changes in neuronal activity. Although tasks based on hemispheric and other known functional localization were chosen, there was little reason *a priori* to expect so large a proportion of neurons to be responsive to a predetermined task, demonstrated here by the high proportion of populations changing activity with the face-matching task. Often neurons change activity with only one or a few of multiple tasks, indicating some degree of specificity. What has been generally missing from these studies are many neurons changing activity in the same way in first or second epoch of all tasks, as might be characteristic of a non-specific effect of attention or arousal, or neurons changing activity in the same way with first epochs of all tasks presented in one modality, as might be characteristic of activity predominantly related to perception in that modality. In addition, nearby neuronal populations, separated by amplitude, commonly change activity with different tasks, as was evident in the present study at five of the six records from a single electrode separable into multiple populations. Such an arrangement may facilitate the development of associations. These findings suggest that human association cortex is compartmentalized into behaviourally specific systems, involving widely dispersed neurons.

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FUNCTIONAL NEUROANATOMY OF FACE AND OBJECT PROCESSING

A POSITRON EMISSION TOMOGRAPHY STUDY

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SUMMARY

Studies of brain-damaged patients have revealed the existence of a selective impairment of face processing, prosopagnosia, resulting from lesions at different loci in the occipital and temporal lobes. The results of such studies have led to the identification of several cortical areas underlying the processing of faces, but it remains unclear what functional aspects of face processing are served by these areas and whether they are uniquely devoted to the processing of faces The present study addresses these questions in a positron emission tomography (PET) study of regional cerebral blood flow in normal adults, using the ^{15}oxygen water bolus technique. The subjects participated in six tasks (with gratings, faces and objects), and the resulting level of cerebral activation was mapped on images of the subjects' cerebral structures obtained through magnetic resonance and was compared between tasks using the subtraction method. Compared with a fixation condition, regional cerebral blood flow (rCBF) changes were found in the striate and extrastriate cortex when subjects had to decide on the orientation of sine-wave gratings. A face-gender categorization resulted in activation changes in the right extrastriate cortex, and a face-identity condition produced additional activation of the fusiform gyrus and anterior temporal cortex of both hemispheres, and of the right parahippocampal gyrus and adjacent areas. Cerebral activation during an object-recognition task occurred essentially in the left occipito-temporal cortex and did not involve the right hemisphere regions specifically activated during the face-identity task The results provide the first empirical evidence from normal subjects regarding the crucial role of the ventro-medial region of the right hemisphere in face recognition, and they offer new information about the dissociation between face and object processing.

INTRODUCTION

The human face holds a special place among visual objects. Any social animal must possess the capacity to differentiate and recognize members of its group and, in humans, the face is the most distinctive attribute for indexing identity reliably. For the face to assume such an indexing role, the processing organism must be endowed with structures and mechanisms adapted to performing the operations required by this function, and this implies a cognitive and structural architecture different from that required in the processing of other objects that are not called to play such a role.

From a cognitive standpoint, there are several ways in which the processing of faces differs from that of other objects. For instance, most objects are processed at the basic category level (Rosch *et al.*, 1976) regardless of the particularities of each object, whereas each instance of faces is treated as different within the category of faces and the differentiation of each face allows access to related stored biographical information.

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In addition, a large diversity of information about an individual can be derived on the sole basis of the physical attributes of a face, irrespective of its identity, and inferences about age, gender, race, emotion, the charm of the face, and so on, can be made that provide valuable information relevant to the bearer of the face. Another way faces differ from other objects, therefore, seems to be the variety of categories into which faces can be classified, with the same facial attributes being processed and combined differently depending on the information one wishes to access about an individual (Sergent, 1989). In contrast, for practical purposes, most objects belong to a single category and do not lend themselves to multiple categorizations.

What makes face recognition a complex process is the large number of instances with which we are confronted, which requires the extraction, from a general configuration common to all faces, of the particularities that make each face unique. This implies refined perceptual mechanisms capable of detecting subtle differences among faces and of achieving a structural representation that uniquely defines each face (Sergent, 1989). Each representation must then be stored reliably, and this imposes added constraints on the processing organism given the many faces which we have to remember. Moreover, for a perceived face to be recognized as familiar, further operations must be implemented to make contact between perceived and stored facial information, and these operations are concerned with extracting the physiognomic invariants embedded in a given facial representation that may take diverse appearances resulting from the variety of possible formats, poses, angles of view, expressions, distance or illumination. Additional processes must then be performed for a face to be identified, and these involve the reactivation of episodic and semantic (i.e. biographic) information related to that face and without which it would remain that of a stranger.

In spite of its complexity, face recognition is an automatic, effortless and quasi-infallible process, and this attests to the high level of efficiency of the cerebral structures sustaining this function. A detailed specification of the anatomical architecture of face recognition has been difficult to achieve, however, and the only source of information bearing on this issue has so far come from the study of prosopagnosic patients. The correlation between, on the one hand, the behavioural impairments related to the inability to process faces and to associated deficits and, on the other hand, the location of the lesions, has offered the opportunity to identify cortical areas the damage of which produced prosopagnosia (Meadows, 1974; Damasio *et al.*, 1982, 1990*a*). Yet the reliance on data from neurological patients to infer the structural and functional organization of the cerebral structures *normally* underlying face recognition is confronted with a series of theoretical and methodological difficulties.

First, enquiring about the location of the lesions responsible for prosopagnosia and asking which cortical areas underlie the normal processes inherent in face recognition are distinct questions that may not have the same answers. For instance, a focal damage may have detrimental effects on the functions of distant intact areas and, within a damaged brain, local structural integrity does not guarantee normal functioning (Monakow, von, 1910; Sergent and Signoret, 1992). Secondly, there is such a large variability among patients in the aetiology and location of the damage associated with the occurrence of prosopagnosia that it has been difficult to achieve a comprehensive view of the biological architecture of face recognition. Thus, even though the ventro-medial occipito-temporal junction of the right hemisphere has been considered a critical area in the processing of faces, cases have been reported in whom the lesion did not invade this particular region (e.g. Damasio *et al.*, 1982; Bruyer *et al.*, 1983; Sergent and Poncet, 1990). Similarly, although it is widely held that bilateral damage underlies the occurrence of prosopagnosia (e.g. Meadows, 1974; Damasio, 1985), cases have been reported whose Magnetic Resonance Imaging (MRI) scans showed no sign of left-hemisphere involvement (*see* Michel *et al.*, 1989, for a review). Thirdly, the problem is further complicated by the fact that prosopagnosia, albeit an essentially selective impairment, has so far *never* occurred in a pure form. Every case of prosopagnosia that has been thoroughly studied displayed associated deficits of a perceptual and/or mnesic nature (*but see* De Renzi, 1986). On the other hand, the occurrence of associated deficits could help refine the identification of the functional locus of prosopagnosia in each individual case (e.g. Sergent and Poncet, 1990), but two factors have so far prevented this possibility. It cannot as yet be established if the non-facial impairments accompanying prosopagnosia result from a common basis to the processing of faces and the other deficient functions or reflect adjacent cortical territories respectively dedicated to different functions but conjointly damaged. Moreover, even though the nature of the prosopagnosic and associated deficits appears to suggest perceptual impairments in some cases and memory impairments in others (*cf* Hécaen, 1981; Sergent and Villemure, 1989), the informative value of such observations has not yet been fully exploited.

It thus seems that the knowledge and understanding of the anatomical substrates of face recognition cannot be entirely achieved on the sole basis of data from prosopagnosic patients. The purpose of the present study is to contribute to a clarification of the anatomical architecture of face recognition and object recognition in the normal brain, using positron emission tomography (PET) measures of regional cerebral blood flow (rCBF) in normal adults performing cognitive tasks of face and object recognition.

Positron emission tomography studies have opened the way to a better understanding of neurobiological substrates of psychological functions and, with short-lived isotopes such as ^{15}O, have led to a localization of cerebral areas activated during the performance of cognitive tasks (e.g. Posner *et al.*, 1988). Although this approach is confronted with numerous technical, methodological and theoretical problems, these will be dealt with in the final discussion, assuming that the PET technique provides sufficiently significant findings not to engage in a critical evaluation of its merits at this point. The approach adopted in the present study is based on the technique developed by Raichle, Fox and Posner (e.g. Petersen *et al.*, 1988; Posner *et al.*, 1988), with ^{15}O as a radioactive tracer and successive and complementary tasks allowing, through the subtraction method, the comparison of the localization and level of cerebral activation as a function of the specific processing demands inherent in the experimental tasks.

Some characteristics of the present approach differ from earlier studies. It consists in the first PET study on face identification, comparing the recognition of faces with that of common objects. In an attempt to identify the cerebral activation specific to face recognition, this particular condition was compared with a condition requiring the processing of another property of faces than identity, namely the gender of faces. Given that gender categorization is typically preserved in prosopagnosic patients (e.g. Tranel *et al.*, 1988; Sergent and Villemure, 1989), a comparison of gender discrimination and face recognition will provide an 'isolation' of the structures specifically involved in the process of identifying faces, rather than performing a comparison of this condition with a rest condition or a passive-looking condition (e.g. Posner *et al.*, 1988) which would result in the activation of cerebral areas not uniquely engaged in the processes of face recognition. In addition, one of the difficulties inherent in the interpretation of PET results lies in the localization of the foci of activation in the cerebral structures. In the present study, functional data from PET scans are superimposed on structural data from MRI scans obtained from each subject. This procedure (Evans *et al.*, 1988) offers the opportunity to identify the cerebral areas activated during the performance of a given task and directly to compare the localization of foci of activation in the normal brain with the site of lesions in the brains of prosopagnosic patients.

This study is thus concerned with clarifying the anatomical substrates of face and object processing, and it addresses a series of specific questions. On what cortical structures does the processing of faces rely? Does the processing of different properties of faces (e.g. gender and identity) engage different cortical structures? Does the processing of faces and objects rely on common anatomical areas? Do findings from a PET study on normal subjects concur with the anatomical and radiological evidence obtained from prosopagnosic patients? What is the respective role of the cerebral hemispheres in the processing of faces and of objects? What is the relation between hemisphere processing contribution as inferred in divided visual-field studies, and the actual involvement of the cerebral hemispheres as indicated by PET measures of cerebral activation?

METHODS

Subjects

Seven male adults, aged between 22 and 31 yrs, participated in the experiment. They were in good health, under no medication, and had no neurological or psychiatric disorders. They were right handed, as assessed with Bryden's (1982) questionnaire, with no left handers among their close relatives, and they had normal visual acuity and contrast sensitivity. They were fully informed of the risks associated with exposure to radioactive material, in accordance with the regulations of the Medical Research Council of Canada and the Control Board of Atomic Energy of Canada, and they read and signed consent forms for their participation They were remunerated $100.

Procedures and equipments

The experiment comprised four phases, described in the order they took place.

Preparatory phase. This phase consisted in introducing the subject to the experiment, explaining the risks, obtaining his formal consent, testing his handedness and vision, and preparing him to the experimental tasks in order to lessen potential anxiety and to reduce hesitations during the experiment proper Each experimental task was explained and run, in conditions identical to those prevailing in the PET study, except that different stimuli were used. The subjects were also requested to fill in a questionnaire containing a list of 250 names of famous persons, and to indicate whether or not the name was familiar, and, if so, whether they could image a representation of the corresponding face and how clear this representation was. The faces used in one condition of the PET study were selected from this list for each subject, using those faces that subjects could represent clearly.

PET experiment. The PET study took place the day following the preparatory phase and consisted in measuring rCBF in six different conditions run at 15 min intervals, with a different order of conditions for each subject. The stimuli were presented on a high-resolution Mitsubishi monitor, driven by a PS/2 IBM computer, in total darkness. The computer also controlled the duration of stimulus presentation (1 s), the interstimulus interval (3 s) and recorded the speed and accuracy of the subject's responses. The monitor was located above the subject's abdomen, at 85 cm from his eyes, and was oriented obliquely so that the screen was perpendicular to the subject's line of gaze. The stimuli appeared in the centre of the screen, and their size (in degrees of visual angle: 8° in height and 6° in width) and luminance were constant across conditions In each condition, 40 stimuli were presented, except for a 'fixation' condition.

The subjects were in a supine position, the head firmly held in a customized frame containing rapidly hardening self-inflating foam-like material and located in the centre of the tomograph scanner. Ears were occluded with wax, and an intravenous catheter was placed into the left brachial vein for injection of $H_2{}^{15}O$ (40 mCi per injection) which served as CBF tracer. In each experimental condition, stimulus presentation started conjointly with the injection of the radioactive solution, and the recording of the emission of positrons began 15 s later and lasted for 60 s. Stimulus presentation went on for one more minute after the end of scanning in order to obtain additional data about the speed and accuracy of the subjects' responses. In four conditions, the subjects responded by pressing, with the index or middle finger of the right hand, one of two buttons of the computer 'mouse' which was placed on their abdomen.

The study comprised three control conditions and three experimental conditions: (1) fixation: the subject looked at a fixation point located in the centre of the screen, and was required to concentrate on this point. The illuminated area of the screen was of the same size and average luminance as the faces and objects presented in the other conditions; (2) passive face-looking: the stimuli were black-and-white faces of individuals unfamiliar to the subjects, half of each gender, which the subject was requested to look at passively, (3) gratings: the stimuli were sine-wave gratings, with spatial frequency varying between 0 2 and 16 cycles per degree of visual angle, and contrast being held constant at 0.5. Half the gratings were oriented horizontally and the other half vertically, and the subject's task was to press one button for one orientation and the other button for the other orientation; (4) gender discrimination: the stimuli were black-and-white faces of individuals unfamiliar to the subjects, half of each gender, which the subject had to categorize as male or female by pressing one of the two buttons; (5) face identity: the stimuli were black-and-white faces of famous persons, drawn from the list presented to the subject the day before, and they were therefore all known by the subjects. Half the faces depicted actors and the other half depicted persons from other professional categories (politicians, sportsmen, newsmen, singers). The subject's task was to decide whether or not the face was that of an actor, and to press one of the two buttons to indicate the response; (6) object recognition: the stimuli were black-and-white photographs of common objects, half of which were 'living' or natural (cat, tree, fish) and the other half 'non-living' or man-made (car, fork, table). The subject had to press one button for one category and the other button for the other category.

It must be noted that the face- and object-recognition tasks are, strictly speaking, categorization tasks, as the specific name or identity of the object or the face does not have to be accessed. However, such a categorization cannot be performed unless the stimulus is actually recognized (e g. Sergent, 1985). In all conditions, and particularly in conditions 5 and 6, the subject was specifically instructed not to name the faces and objects, neither explicitly or implicitly, nor to attempt to retrieve their names. However, after the preparatory phase, the PET experiment, and the subsequent divided visual-field study, all the subjects commented that they had been unable to refrain from thinking of the names of the famous faces and of the objects

Divided visual-field study. This phase took place between 2 and 4 wks after the PET study. It consisted in a divided visual-field experiment using the same conditions and stimuli as in the PET study, without PET scanning and with two main differences. Only the conditions 3 to 6 were tested (i.e. gratings, gender discrimination, face identity, and object recognition). The stimuli were presented twice, once in each visual field at an eccentricity of 5° of visual angle, resulting in the presentation of 80 stimuli in each condition.

To ensure as much similarity of stimulus presentation in this and the PET experiments, the same monitor, computer, stimulus duration and interstimulus interval were used in the two studies. Because of the lateral presentation, the size of the stimuli was reduced by half; however, to keep the actual visual angle of the stimuli the same in the two studies, the subjects viewed the stimuli from half the distance used in the PET experiment (43 cm). In addition, the stimuli were presented for 1 s as in the PET study. This made it necessary to control for eye fixation in the centre of the screen in order to ensure that the laterally presented stimuli would effectively be projected to the contralateral hemisphere. This was achieved on-line with a Gulf and Western (Model 1994B) Eye-View-Monitor system using corneal reflection to determine the locus of fixation. Before the experiment, central fixation was established for each subject, and the digital coordinates of central eye position were entered in the computer. During the experiment, eye position was sampled every 16.7 ms. Stimulus presentation required five consecutive samples of eye position to be within 0.5° of visual angle of the central fixation coordinates; any departure of more than 0.5° would delay stimulus presentation and, during the 1 s of exposure, would interrupt the presentation of the stimulus, in which case the trial was discarded This procedure guaranteed that initial stimulation was projected to the contralateral hemisphere. Subjects were very accurate in maintaining central fixation, and less than 1% of the trials had to be discarded because of eye deviation from the centre.

MRI study. This phase took place immediately after the laterality study. It consisted in a MRI scan of each subject's brain, with a Philips Gyroscan (1.5 Telsa), using the same head-holder and the same orientation of the head as for the PET scan

Scanning and analyses

PET scanning was performed by measuring rCBF using the intravenous ^{15}oxygen water bolus technique (Raichle *et al.*, 1983) and a Scanditronix PC-2048 PET scanner with in-plane and spatial resolutions of 5–6 mm full width at half maximum. Fifteen slices with a centre-to-centre distance of 6.8 mm were simultaneously imaged, which could be further divided by bilinear interpolation to produce 80 transaxial slices. A rotating ^{68}germanium source was used to correct the images for attenuation of the gamma rays in the skull and brain tissue. The image planes were chosen parallel to the subject's glabella-inion line which was aligned with the tomograph's laser reference line and transcribed onto the head-holder as a marker for the correlation of PET and MR imaging. The MR images were obtained at the same 15 planes as in the PET study. Slice registration was ensured using a thin $CuSO_4$-filled (5 mm) catheter attached to the side of the customized head-holder, and visible in an MR image, coincident with the reference line identifying the PET scan reference plane (Evans *et al.*, 1989).

The PET activation functional images were mapped onto the MR structural images using a PIXAR three-dimensional computer and landmark-matching software (Evans *et al.*, 1989). Interactive three-dimensional image software was used to establish an orthogonal coordinate frame based on the anterior commissure-posterior commissure (AC-PC) line as identified in the MR image volume. These coordinates were used to apply a linear resampling of each matched pair of MRI and PET datasets into a standardized stereotactic coordinate system (Talairach and Tournoux, 1988). PET images were then normalized for global CBF and the difference between control and experimental conditions determined for each subject. The mean state-dependent change image volume was obtained by averaging across subjects (Fox *et al.*, 1985) and then converted to a *t*-statistic by dividing the mean state-dependent change by the mean standard deviation in normalized CBF for all intra-cerebral voxels and by multiplying this quotient by the square root of N (number of subjects). Anatomical and functional images were merged to allow direct localization on the MR images of *t*-statistic peaks identified by an automatic peak-detection algorithm (Mintun *et al*, 1989) and for the anatomical correlation of extended zones of activation not expressible in terms of isolated peaks The peak distribution was then searched for significant signals using change-distribution analysis (Fox *et al.*, 1988, Fox, 1991) and *z*-score thresholding. Peaks with significance levels of $P < 0.05$ are reported

RESULTS

Two main sets of data were collected in this investigation, one in the PET study, and the other in the divided visual-field study, and they will be discussed in turn.

PET study

The PET study comprised three control and three experimental conditions. However, the passive face-looking condition turned out to be inadequate as a control and, compared with the grating condition, resulted in no significant change in activation. This can be attributed to the variety of information conveyed by faces, which implies that faces lend themselves to a diversity of cognitive operations, and the subjects thus had the possibility to consider different properties of the faces during this condition. This suggests that a passive-looking condition, often used in PET studies (e.g. Posner *et al.*, 1988), may not always serve as an adequate control given the impossibility to determine the cognitive operations actually performed by the subjects in the absence of specific instructions.

The results of the other four conditions (gratings and the three experimental conditions) proved reliable as response accuracy was controlled and subjects did perform the requested tasks. In each condition, each subject's response accuracy was equal or superior to 95%, except in the face-identity condition in which accuracy dropped to 85% in two subjects.

The grating condition served as control for the experimental conditions, and the experimental conditions on face processing were compared with one another. The significant foci of activation are presented in Table 1, expressed in terms of Talairach and Tournoux's (1988) stereotactic coordinates, of their location in Brodmann's classification and of the common name of the activated area. The most significant foci of activation are shown in Fig. 1, superimposed on a MR image of the brain. Cerebral

TABLE 1 LOCALIZATION OF FOCI OF ACTIVATION WITH THE SUBTRACTION METHOD, EXPRESSED IN TERMS OF STEREOTACTIC COORDINATES, BRODMANN'S CLASSIFICATION AND USUAL NAME OF CORTICAL AREA

Coordinates					
X	*Y*	*Z*	*Brodmann's area*	*Cortical area*	*Level of significance*[1]
Gratings–Fixation					
3	−82	3	Right 17	Striate cortex	**
8	−87	9	Right 17	Striate cortex	***
−12	−77	8	Left 17	Striate cortex	***
−7	−85	6	Left 17	Striate cortex	***
4	−81	2	Right 18	Lingual gyrus	***
12	−79	2	Right 18	Lingual gyrus	***
−27	−98	−6	Left 18	Inferior occipital gyrus	*
15	−82	30	Right 19	Parieto-occipito sulcus	**
−19	−81	32	Left 19	Parieto-occipito sulcus	*
−41	−28	59	Left 3	Primary sensory area	***
−44	−35	60	Left 1	Secondary sensory area	**
−41	−18	62	Left 4	Motor area	***
−33	−2	60	Left 6	Premotor area	**
Gender discrimination—gratings					
19	−92	18	Right 19	Cuneus	**
40	−77	−2	Right 18	Inferior occipital gyrus	*
43	−73	−2	Right 19	Inferior occipital-temporal gyrus	*
29	−81	−8	Right 19	Lateral occipital gyrus	*
−32	−73	−3	Left 19	Middle occipital gyrus	*
20	−81	−6	Right 18	Lingual gyrus	*
Face identity—gender discrimination					
−23	−3	−32	Left 36	Medial anterior temporal gyrus	**
25	−5	−32	Right 36	Medial anterior temporal gyrus	***
37	20	−32	Right 38	Temporal pole	**
−36	9	−27	Left 38	Temporal pole	**
24	−15	−20	Right 36	Parahippocampal gyrus	***
−3	25	−17	Centre 11	Gyrus rectus	**
−37	−60	−12	Left 37	Fusiform gyrus	*
37	−55	−11	Right 37	Fusiform gyrus	**
−52	−9	−9	Left 21	Middle temporal gyrus	**
21	−60	2	Right 18	Lingual gyrus	*
Object—gratings					
−55	−39	−17	Left 20	Inferior temporal gyrus	**
−37	−58	−14	Left 37	Fusiform gyrus	**
−53	−9	−11	Left 21	Middle temporal gyrus	**
−40	−76	−6	Left 19	Middle occipital gyrus	**
−32	−60	60	Left 7	Superior parietal lobe	*
52	−23	32	Right 40	Supramarginal gyrus	*
−53	−18	18	Left 40	Supramarginal gyrus	*
−2	21	−19	Centre 11	Gyrus rectus	*

[1] ***$P < 0.001$, **$P < 0.01$, *$P < 0.05$

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localization is described along the three Euclidean axes: X corresponds to the lateral axis, 0 being the midline between two hemispheres and negative values indicating the left hemisphere; Y corresponds to the antero-posterior axis, 0 being at the level of the anterior commissure and negative values indicating the posterior regions; Z corresponds to the dorsoventral axis, 0 being at the level of the AC-PC line and negative values indicating areas below this line.

Gratings minus fixation. The perception of the gratings, and their categorization as a function of their orientation signalled by a right-hand response, resulted in intense activation of the primary visual cortex and the left pre- and post-rolandic areas corresponding to the cortical representation of the right hand (Fig. 1).

The main foci of activation were located in the striate cortex of both hemispheres, in the posterior part of the right lingual gyrus (area 18) and in the inferior lateral occipital area of the left hemisphere (area 18). All these cortical regions were equally activated in the three experimental conditions, and they reflect elementary perceptual operations, irrespective of the complexity and signification of the visual information being processed. The only cortical area activated by the presentation of the gratings and not by other visual stimuli was located in the occipito-parietal sulcus of both hemispheres (area 19, *see* Table 1), and this activation can therefore be attributed to the spatial discrimination inherent in the categorization of the gratings as a function of their orientation.

A second focus of activation was specific to the right manual response and is presented in the central left part of Fig. 1. It is located in the pre- and post-central superior region of the left hemisphere encompassing the primary and secondary sensorimotor areas, and it was also present in the three experimental conditions that too required a right manual response.

Gender categorization minus gratings. Gender categorization was tested with faces unfamiliar to the subjects, and this task does not require the identification of the faces nor does it call for the processing of faces as unique entities. This condition resulted in further activation of extrastriate visual areas 18 and 19, and the involved cerebral structures were more anterior and more ventral than those activated during the categorization of the gratings. However, the gender discrimination task also engaged the right cuneus as well as the lateral occipital area of the left hemisphere (area 19, *see* Table 1).

Face identity minus gender categorization. All the cortical areas specifically activated during the face-identity task were located more anteriorly than those engaged in the face-gender categorization task, as indicated by the location of these areas on the antero-posterior Y axis (*see* Table 1). In addition, both hemispheres participated in the operations underlying face identification, but asymmetrically so. In the occipital and posterior temporal cortices, the right lingual gyrus (area 18), the fusiform gyrus of both hemispheres (areas 19 and 37), and the middle gyrus (area 21) of the left temporal cortex were significantly activated during the face-identity task. The highest level of activation was found in the parahippocampal gyrus (area 36) of the right hemisphere, and no activation of the homotopic area of the left hemisphere was observed (*see* Fig. 1, at level −20 on the Z axis). Also activated during the face-identification task were the most anterior regions of the temporal cortex, including the temporal pole of both hemispheres and the adjacent medial areas, as illustrated in Fig. 1. All these foci of activation are localized in the ventral parts of the cortex, as indicated by their values on the dorsoventral plane

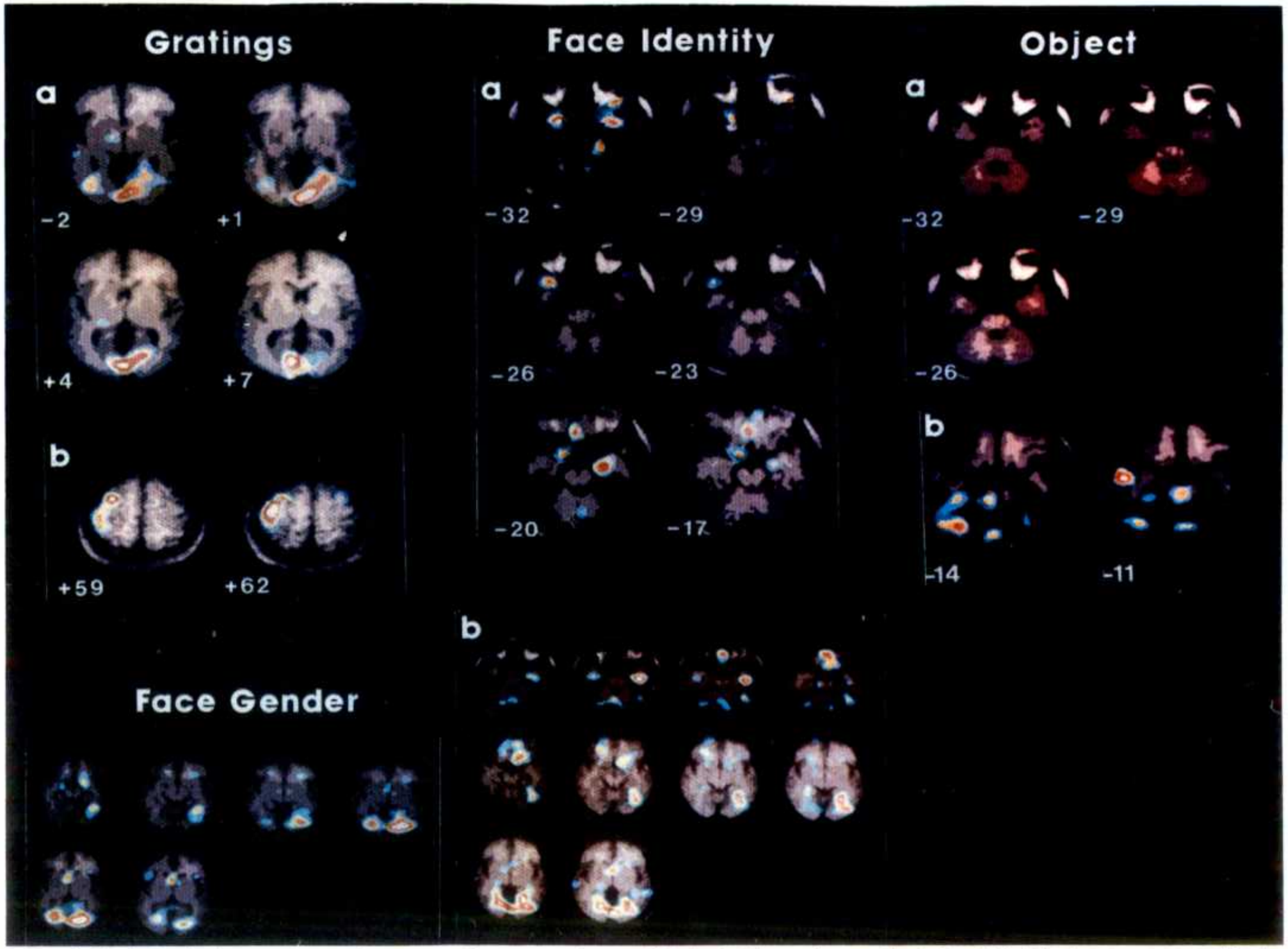

FIG. 1. Foci of activation superimposed on a magnetic resonance image of the brain (the numbers on the bottom left of the images correspond to the slice level on the Z axis). Gratings: gratings minus fixation (*a*) activation at the level of the occipital cortex; (*b*) activation at the level of the left sensorimotor cortex. Face gender: face gender minus fixation; slices are 3 mm apart, starting at $Z = -8$. Face identity: (*a*) face identity minus face gender; (*b*) face identity minus fixation; slices are 3 mm apart, starting at $Z = -23$. Object: object-recognition minus gratings (*a*) absence of activation of the anterior temporal cortex; (*b*) activation of the left occipito-temporal cortex and the left temporal area 21.

(*see* Table 1), and, except for the left temporal area 21, no significant activation was detected in the lateral parts of the cortex.

A last area of significant activation was found in the gyrus rectus (area 11) of both hemispheres, which is part of the orbitofrontal cortex.

Objects minus gratings. The categorization of objects, in addition to the areas activated during the classification of the gratings, resulted in significant increased activity in cortical regions of the left hemisphere (*see* Table 1). This was observed in the lateral occipito-temporal areas 19 and 20, and in the superior parietal lobule (area 7). In addition, other foci of activation indicated the involvement of the supramarginal gyrus (area 40) of both hemispheres, of the left middle temporal area (21) and of the gyrus rectus (area 11), the latter two also activated in the face-identity task.

Comparison of face- and object-recognition conditions. In order to identify the cerebral areas specifically activated during the face- and the object-recognition tasks, respectively, these two conditions were compared with one another. A subtraction of the object condition from the face-identity condition resulted in no statistical significance change in the areas of the right hemisphere activated during the recognition of faces, except for the right lingual gyrus (+2 on the Z axis), suggesting no specific involvement of the right fusiform, parahippocampal and anterior temporal areas in the categorization of objects. In contrast, this subtraction indicated that the activation observed in the posterior areas of the left hemisphere (areas 37 and 21), and of the gyrus rectus (area 11) during the face-recognition tasks was no longer apparent when compared with the object-recognition task, suggesting an involvement of these three regions in the two tasks. Nonetheless, the significant activation of the anterior regions of the left temporal cortex (areas 36 and 38) was not modified by this subtraction. The reverse subtraction (object minus face identity) eliminated all significant activation changes mentioned earlier for the object-recognition task, except in the areas 19 and 20 of the left hemisphere that were therefore not significantly engaged during the face-recognition condition.

Divided visual-field study

In this study, the subjects performed a reaction-time task on the four categories of stimuli used in the PET study, and the stimuli were presented in the retinal periphery. Reaction times and percentage of errors in the four conditions, averaged across subjects, are shown in Table 2 as a function of visual field. A repeated-measure analysis of variance was conducted on these data, with visual field and task as independent variables. The analysis of reaction times indicated that the main effect of visual field was not significant [LVF: 794 ms; RVF: 796 ms; $F(1,6) < 1$], whereas the main effect of task was highly significant, with the face-identity task yielding significantly longer reaction times than the other three tasks [$F(3,18) = 17.43$, $P < 0.01$]. More important, the interaction of task by visual fields was significant [$F(3,18) = 12.72$, $P < 0.01$], indicating a different pattern of visual-field asymmetries in the four tasks. The simple effects of this interaction were analysed with Tukey's HSD test. The visual-field difference was not significant in the gratings nor the object conditions ($P > 0.20$), but was reliable in the face-gender (LVF: 722 ms; RVF: 757 ms; $P < 0.01$) and in the face-identity condition (LVF: 941 ms; RVF: 922 ms; $P < 0.02$).

The same analysis of variance performed on the error data indicated a main effect of task ($P < 0.01$) similar to that found in the analysis of reaction times. No other effect was significant, but the pattern of errors paralleled the results of the reaction-time data, suggesting no speed-accuracy trade off. The only difference between visual fields to approach significance was found in the face-identity task (LVF: 7.5%; RVF: 4.2%; $P < 0.085$).

TABLE 2 MEAN REACTION TIME (IN MS), PERCENTAGE OF ERRORS, AND STANDARD DEVIATION IN THE DIVIDED VISUAL-FIELD STUDY AS A FUNCTION OF TASK AND VISUAL FIELD

	Gratings		*Gender*		*Face identity*		*Objects*	
	LVF	*RVF*	*LVF*	*RVF*	*LVF*	*RVF*	*LVF*	*RVF*
RT	740	740	722	757	941	922	774	764
Errors	2.4	1.8	0.6	0.9	7.5	4.2	3.3	3.1
SD	124	118	109	127	131	129	101	105

LVF = left visual field; RVF = right visual field, RT = reaction time

Because each of the 40 stimuli was presented twice in the divided visual-field study, the data are not directly comparable with those of the PET study in which each stimulus appeared only once. Accordingly, an additional analysis was carried out on the reaction times of the face-identification and the object-categorization tasks, in order to examine the pattern of visual-field differences for the first presentation of each stimulus. A three-way analysis of variance was thus conducted, with factors being task (face vs object), visual field (left vs right) and order of presentation (first vs second). In this analysis, 'first' refers to the first presentation of a face or an object in one visual field, and comprises 20 stimuli in each condition and visual field. The results are shown in Table 3. The main effects of task and order of presentation were significant ($PS < 0.01$), with objects being responded to faster than faces, and the second presentation yielded faster reaction times than the first presentation. The main effect of visual field was not significant ($F < 1$). Among the two-way interactions, only one reached a reliable of significance, that of visual field by order of presentation [$F(1,6) = 9.57$, $P < 0.02$], and it indicated that an initial superiority of the left visual field (LVF: 944 ms; RVF: 952 ms) was replaced by a right visual-field advantage in the second presentation (LVF: 771 ms; RVF: 734 ms). However, this interaction was due entirely to a shift in visual-field advantage from the first to the second presentation in the face-identity task, indicated by the significant three-way interaction [$F(1,6) = 8.42$, $P < 0.05$], as reaction times were faster to left (1037 ms) than to right (1068 ms) visual-field trials in the first presentation, and were faster to right (776 ms) than to left (845 ms) visual-field trials in the second presentation of the faces.

TABLE 3 MEAN REACTION TIMES (IN MS) IN THE FACE-IDENTITY AND THE OBJECT-CATEGORIZATION TASKS, AS A FUNCTION OF VISUAL FIELD AND ORDER OF PRESENTATION OF THE STIMULI

Face identity		*Objects*	
LVF	*RVF*	*LVF*	*RVF*
1037	1068	851	836
845	776	697	692

DISCUSSION

The purpose of this study was to identify, in normal subjects, the anatomical substrates of face and object processing, and the results provide new information about the participation of cortical areas in the operations underlying the realization of these functions. These results offer the possibility to clarify some questions bearing on (1) the functional neuroanatomy of face processing; (2) the critical cortical areas the damage of which produces prosopagnosia; (3) the structural and functional dissociation of face and object processing; (4) the respective contribution of the cerebral hemispheres to these functions. Each of these points will be discussed in turn, and will then lead to a critical evaluation of the contribution of PET studies to the understanding of the structural and functional organization of cognitive functions.

Functional neuroanatomy of face processing

The neurobiological substrates of cognitive functions have been uncovered through anatomoclinical studies of brain-damaged patients selectively impaired in specific functions. One problem inherent in the interpretation of such impairments results from the difficulty in determining the relation between the site of a lesion and its behavioural or cognitive manifestations, and, therefore, in identifying the contribution of the damaged area to the realization of a given function. A priori, PET studies in normal subjects are immune to such difficulties, and the recorded foci of activation may be attributed to the participation of specific cortical areas in the underlying operations, without interference by a damaged structure on adjacent or remote intact areas. It can therefore be assumed that an activated area, identified by PET scanning and resulting from a significant increase in cortical activity from one condition to another, constitutes a valid indication of the participation of this area in the operations distinguishing the two conditions. However, the interpretation of anatomical data obtained by PET measures of cerebral activation is confronted with difficulties inherent in this approach. First, these data may not necessarily allow an unequivocal identification of the functional properties of each activated area, especially when the function under study engages complex and numerous cognitive operations, as is typically the case of face identification. Secondly, the *participation* of a given area in performing a given function does not necessarily imply that this area is *indispensable* to the realization of that function. Therefore, the interpretation of the present PET data requires comparison with findings from other sources.

Anatomical data. At a purely anatomical level, a first conclusion, illustrated in Table 1, concerns the large cortical volume activated during the processing of faces. Even if all the involved areas are not specific to face processing, the activated regions extend from the occipital to the temporal poles, and engage the ventro-medial parts of the brain. This extensive neuronal network underlying the processing of faces may appear disproportionate given the multitude of other functions carried out by the brain, and it may be suggested that this large cerebral space inherent in the processing of faces, essential in human social and interpersonal relationships and involving complex cognitive operations, is necessary for face identification to be achieved with such efficiency and apparent automaticity.

On the basis of the results from the *face-gender categorization* task, the ventral part of the occipital cortex appears to play a critical role in the perceptual operations on facial information, and the areas activated during this task were not involved in the grating-discrimination nor in the object-categorization tasks. In addition, the results point to a predominant contribution of the right ventral areas of the extrastriate cortex in these perceptual operations, whereas the homotopic region of the left hemisphere was not significantly activated. Nonetheless, this particular task did engage the left occipital cortex, and a significant activation of the lateral area 19 was apparent in a region that was also active in the object-categorization task.

The cortical areas specifically activated during the *face-identification* task were located in more anterior parts of the brain. They comprise the right lingual gyrus and the fusiform gyrus of both hemispheres. It was, however, in the right parahippocampal gyrus and in the ventro-medial region of the right anterior temporal lobe that the highest levels of activation were recorded, and no significant activation of the left parahippocampal gyrus was detected. Nonetheless, the most anterior regions of the temporal cortex of both hemispheres were activated. On the other hand, three foci of activation were common to face recognition and object categorization in the temporal cortex (fusiform gyrus and middle lateral cortex of the left hemisphere) and in the orbitofrontal cortex of both hemispheres.

The participation of the left fusiform gyrus in both face and object processing suggests the involvement of similar visual analysis operations in the two tasks. However, the fact that the face-identification task, but not the object-categorization task nor the face-gender discrimination task, activated the right fusiform gyrus may indicate that this structure performs perceptual operations particularly well adapted to the processing of facial identity. This different pattern of activation in the three experimental tasks is consistent with evidence of qualitatively different processes underlying the extraction of different properties of faces (Sergent, 1985) and the recognition of faces and common objects (e.g. Diamond and Carey, 1986; Biederman, 1987), and it may account for the occurrence of dissociations between face-gender discrimination and face identification (e.g. Tranel *et al.*, 1988) and between prosopagnosia and visual object agnosia, even when prosopagnosia results from a lesion restricted to the right occipital cortex (e.g. Lhermitte and Pillon, 1975).

An interpretation of a common participation of the left middle temporal gyrus (area 21) appears to be less unequivocal on the sole basis of the data from the present experiment. No activation of this area was detected during the grating and the face-gender tasks, which could suggest that its participation does not reflect the implementation of purely visual operations. However, face identification and object categorization require more complex perceptual operations than those needed in the performance of the other two conditions, and, in the same way that the left fusiform gyrus became involved only in the face-identification and object-recognition tasks, the participation of area 21 may reflect the involvement of refined perceptual operations necessary for these recognition tasks. Moreover, in a recent PET study of visual shape discrimination, Corbetta *et al.* (1990) reported an activation of the left area 21 which they attributed to the operation of perceptual processes specific to the analysis of visual shapes.

Such an interpretation may not be entirely satisfactory, however. First, damage to this area does not result in prosopagnosia nor visual object agnosia, and its location, close to secondary auditory areas and distant from the occipital cortex, does not make it an appropriate site for the realization of purely visual analysis operations. Secondly, there is evidence that this part of the temporal cortex may be involved in the naming of visual objects. For instance, Flude *et al.* (1989) reported the case of a patient (E.S.T.) with damage to the left middle temporal cortex who had no deficit at recognizing faces and objects but was unable to retrieve their respective names. Similarly, Damasio *et al.* (1990*b*) have presented data from a patient with cerebral damage in the left temporal area 21 who could not provide the names of visually presented objects but was nonetheless capable of describing their functions and how they should be used, an indication that these objects had been effectively recognized on the basis of the visual attributes. The results of these two studies suggest that the destruction of the left area 21 does not impair the visual recognition of objects as such but the subsequent operations by which a face or an object receives its proper label. It can therefore be suggested that the activation of the left area 21 in the present study may reflect the evocation of the faces and objects' names during the recognition process rather than the operation of purely visual processes inherent in recognition. This suggestion is compatible with current knowledge about the functional organization of semantic and lexical information related to faces and objects. As shown by Semenza and Zettin (1988), a name is an arbitrary label that adds nothing to the knowledge of an object or a face, and the dissociation, frequently observed in brain-damaged and in normal subjects, of an inability to name a face that is nonetheless recognized (e.g. Young *et al.*, 1985; Ellis *et al.*, 1989; Cohen, 1990; Sergent, 1990) clearly indicates that semantic and lexical information is not represented in the same regions of the brain.

A last cortical area activated during both the object and the face-identity tasks was the gyrus rectus, in the orbitofrontal cortex. This activation was absent in the other two conditions, and therefore cannot be attributed to the manual response as such nor to the two-choice decision, as these two factors were included in the four conditions. In addition, this activation cannot be attributed to the processing of faces *per se*, and the fact that it occurred in tasks requiring different types of semantic categorization indicates that it is not specific to a unique cognitive operation. It is therefore unclear what the source of this activation may be, and there is little evidence from the study of humans bearing on the role of this area. On the other hand, Bachevalier and Mishkin (1986) have shown in the monkey that the destruction of the ventro-medial region of the frontal cortex, including the gyrus rectus, resulted in impaired recognition of visual objects, and they suggested an involvement of this area in the processes underlying visual memory. Further experimentation is certainly needed to uncover the nature of the actual contribution of the gyrus rectus to the processes of visual recognition.

Another finding of the present experiment concerns the absence of activation of the superior temporal sulcus (STS) of either hemisphere in the face-identity task, whereas electrophysiological recordings in monkeys have revealed the existence of neural cells, located in the STS, selectively responsive to the presentation of simian or human faces (e.g. Perrett *et al.*, 1982; Rolls, 1989). There was no indication in the PET study that this area was in any way participating in the operations underlying the processing of faces. Although null results must be considered with caution, the present findings suggest no involvement of the STS in the processing of faces in humans, and preliminary data from new PET studies on face identification (Sergent, unpublished observations) resulted in a similar absence of activation of this area. Moreover, evidence from prosopagnosic patients unequivocally shows that the lateral part of the temporal cortex is neither necessary nor sufficient to produce prosopagnosia. In fact, in addition to the problem of homology of human and simian cerebral structures, the actual involvement of rostral STS neurones in face recognition has been disputed, as bilateral lesion of this structure in monkeys does not result in impaired face recognition (Cowey and Heywood, 1992).

Anatomical data and prosopagnosia. The present data point to a critical role of the ventro-medial cortex of the right hemisphere and the most anterior region of the temporal lobe of both hemispheres. Neuro-pathological and radiological data from prosopagnosic patients provide information compatible with these findings (Damasio *et al.*, 1990*a*), although, as noted in the Introduction, the empirical data from the patients do not lend themselves to an unequivocal interpretation. Nonetheless, two characteristics of the anatomical basis of face processing seem to be established by now and should not be controversial: (1) the medial occipito-temporal junction plays a critical role in face processing, and this was confirmed in the present study; (2) the right hemisphere makes a predominant contribution to this function, as indicated by the present results and in a recent review of the literature by Michel *et al.* (1989). However, it remains unclear (1) whether the left hemisphere is indispensable for an optimal processing of faces; (2) why the left hemisphere was found to be activated in the PET study when cases of prosopagnosia have been reported to suffer from lesions restricted to the right hemisphere; (3) what operations are subserved by the diverse cortical areas of both hemispheres.

The PET results suggest a bilateral participation of the ventro-medial occipito-temporal junction in face processing, underlying the visual perceptual operations, but this bilateral participation was not symmetrical. The occipito-temporal junction of the right hemisphere appears to be particularly well adapted to sustain perceptual operations on faces as they were not activated during the object-categorization task. On the other hand, the occipito-temporal junction of the left hemisphere, active during the face-gender and face-identity tasks, must perform perceptual operations not specific to the processing of faces as they were also activated during the categorization of objects. There is therefore a predominant, and probably essential, role of the posterior right hemisphere in the perceptual processing of faces, which may be attributed to the demands inherent in face processing and not required by a between-object categorization, namely the extraction of the configurational physiognomical properties that make each face unique.

Nonetheless, face processing did engage the left posterior hemisphere in the normal subjects, but there are reasons to believe that its participation may not be indispensable and that its significant contribution may be conditional to the conjoint involvement of the right hemisphere. These suggestions are based on the existence of cases of prosopagnosia resulting from unilateral right posterior lesion (Michel *et al.*, 1989), implying that the left hemisphere cannot, on its own, assume all the perceptual operations required for the processing of faces. Moreover, there is at present no report of cases of right-handed prosopagnosics whose lesion was restricted to the left hemisphere, and patients with such lesion show no major deficit in face identification. Additional evidence of the limitations of the posterior left hemisphere in implementing the required perceptual operations inherent in face processing is suggested by the results of a recent study by Sergent and Signoret (1991). They had three prosopagnosic patients, whose brain damage was restricted to the right hemisphere, learn the correct association between 12 faces and their respective names, and each patient succeeded in learning such associations after a large number of trials. When tested the next day for their memory of these associations, each patient performed at a high level of accuracy (11 or 12 correct responses), indicating that the connections between each of the faces and their names were properly established; however, when different versions of the learned faces were then presented, the patients' performance dropped to chance, suggesting that they were unable to achieve the required perceptual operations to extract the physiognomical invariants unique to each face. It thus seems that an intact left hemisphere is not equipped with the structures required to perform the perceptual analysis of the configurational properties of faces, and only the right hemisphere can achieve such perceptual operations. This issue will be further discussed when considering the results of the divided visual-field study.

One major finding of the present PET study concerns the high level of activation recorded in the right parahippocampal gyrus during the face-identity task. No other experimental condition gave rise to an activation of this area. Yet, in the existing literature, the parahippocampal gyrus has seldom been identified as a critical region in the occurrence of prosopagnosia, although an examination of the radiological data indicates that it is often involved (Damasio *et al.*, 1990*a*; McCarthy and Warrington, 1990). In fact, the parahippocampal gyrus constitutes an area of convergence located in a key position for bringing together perceptual and memory information. For one thing, it receives a large input from the ventro-medial pathway carrying visual information via the lingual and fusiform gyri (Van Essen and Anderson, 1990). For instance, Michel *et al.* (1989) described the case of a prosopagnosic patient (P.C.) whose lesion destroyed the white matter of the right fusiform gyrus but spared the parahippocampal gyrus. Nonetheless, a PET study of cerebral metabolism in this patient revealed an absence of metabolic activity in the right parahippocampal gyrus, suggesting that this area was partly dependent on input from posterior ventral structures. That is, even when the parahippocampal gyrus is structurally intact, damage to posterior adjacent areas deprives this gyrus of afferent information and makes it functionally disturbed. For another, anatomical studies on the connections of this gyrus with other cerebral structures (Van Hoesen, 1982) have shown its critical role in the establishment and distribution of memory information. On the one hand, the parahippocampal gyrus is a necessary relay station for the transmission of perceptual information toward the hippocampus without which there would be no permanent storage of information within the cerebral structures (Squire, 1987). On the other hand, it is a necessary relay station for the reception of information processed in the hippocampus, and it redistributes this information throughout the association cortex, the limbic system and the anterior temporal cortex. The parahippocampal gyrus, which is an integral part of the limbic system, thus plays a pivotal role by reactivating the connections between afferent information and the semantic, episodic and emotional information that was evoked during earlier perceptions and by re-creating a network of activation by which the incoming information acquires its meaning. What makes this area particularly crucial in face recognition comes from the fact that faces, contrary to other objects which are processed as a function of their category irrespective of their uniqueness, can be identified as representing unique individuals only if they reactivate a minimum of biographical information related to the individual.

The involvement of the most anterior parts of the temporal cortex of both hemispheres observed in the present study may thus reflect the activation of this biographical information related to faces. Only recently has the role of these areas as a depository of personal information about unique entities or individuals been clearly demonstrated. For instance, Ellis *et al.* (1989) reported the case of a patient with damage to the anterior part of the right temporal cortex who was defective at retrieving information about people and monuments, not only from a visual presentation of these entities but also from the evocation of their names, thus suggesting that the information is not specific to faces as such but to the individual entity. It is, however, unclear at this point whether both anterior temporal cortices have an equal essential role to play in these processes, or whether they divide their respective competence along the classical verbal/non-verbal dichotomy (e.g. Tranel, 1991), and further investigation is necessary to clarify this point.

The present results therefore indicate that face identification requires the functional integrity of three specific cortical regions: the right lingual and fusiform gyrus, the right parahippocampal gyrus, and the anterior temporal cortex, possibly of both hemispheres. This localization is still relatively coarse, however, and each of these areas comprises several substructures that may not all be implicated in the processing of faces. In fact, the cortical activity observed in the PET study was focalized in specific parts of these areas rather than encompassing their entire extent (*see* Fig. 1).

It would nonetheless be premature at this point to suggest a more precise localization, within each activated area, of the structures specifically engaged in face processing, and additional experimentation is needed to guarantee the robustness and validity of the present findings. However, these findings clearly show that the recognition of faces calls for the activation of specific structures, each carrying out essential operations, and deficits in face recognition may thus result from lesions localized in different parts of this network, then producing a prosopagnosia the nature of which is a function of the site of the lesion (*see* Damasio *et al.*, 1990*a*; Sergent and Poncet, 1990, for detailed discussions). This suggestion, however, does not imply that these structures are exclusively specialized for the processing of faces. They are specialized for specific operations involving fine discrimination among instances of an object category, evocation of relevant biographical, historic or personal records unique to an individual entity, and therefore the storage of these informational records. As it turns out, faces constitute the prototypical category of objects calling for such processing demands but any object category requiring these operations, as a result of professional needs or personal interests, is susceptible to activate the same cortical structures as those underlying the processing of faces.

Functional neuroanatomy of object categorization

Two main aspects of the results from the object-categorization condition are worth mentioning. One is concerned with the complete absence of activation of the anterior temporal cortex during this task, by contrast to the face-identity task (*see* Fig. 1). This reflects and illustrates the fundamental difference, described in the Introduction, between the processing demands of object and face recognition. Contrary to face recognition, object recognition does not require the activation of biographical information and can be performed through an extraction of the object's invariant attributes that uniquely define its category, irrespective of what makes this instance unique. This distinction is not absolute, however, and some objects may acquire a status similar to that of faces, such as our personal objects, famous animals or historical monuments, in the sense that they are considered as unique entities, distinct of all others belonging to the same category. Such objects may then fail to be recognized by prosopagnosic patients, especially if their lesion involves the anterior part of the temporal cortex (*cf* Ellis *et al.*, 1989). For instance, the prosopagnosic patient P.V. described by Sergent and Poncet (1990) and whose lesion occupied the anterior temporal cortex of both hemispheres, was unable to recognize such famous monuments as the Eiffel Tower and the Arc de Triomphe, as well as her own handwriting, but had no difficulty recognizing usual objects at the category level.

A second point bears on the predominant contribution of the left hemisphere in object recognition, beyond the elementary perceptual operations subserved by the striate and pre-striate cortex of both hemispheres. The functional organization of the cortex thus dissociates objects from faces, even if some cortical structures participate in the processing of both of them, such as the left fusiform gyrus. This finding provides some clarification of an often debated issue in the study of agnosias. For instance, Bauer and Rubens (1985) suggested that visual object agnosia and prosopagnosia were normally associated, and they could find no fundamental distinction between the origin of these two deficits. However, these two deficits are associated only in patients presenting with a bilateral posterior lesion, involving the occipito-temporal junction of both hemispheres, whereas prosopagnosics exhibiting no visual object agnosia either have a unilateral right posterior lesion or have a bilateral lesion sparing the left posterior cortex.

The present PET finding on object categorization suggests that the processing of objects to access their meaning can unfold directly from bilateral sensory operations to left-hemisphere based operations, with no need for a right-hemisphere contribution, at least with respect to prototypical canonical views of objects. This finding confirms Warrington's (e.g. McCarthy and Warrington, 1990) suggestion that visual-object categorization at a semantic level may not require the involvement of the right hemisphere. It must be noted, however, that a right posterior lesion responsible for prosopagnosia may disturb the recognition of objects presented in a non-canonical perspective (Warrington and Taylor, 1978). A recent examination of three prosopagnosic patients (Sergent and Signoret, 1991), none of whom had damage in the posterior left hemisphere, showed that they were all defective at recognizing objects seen from a non-canonical perspective (*cf* Landis *et al.*, 1988) whereas they recognized perfectly the same objects seen from a canonical perspective. The contribution of the right hemisphere to object recognition thus becomes crucial when perceptual operations involving corrections, transformation or rotation of the incoming stimulus have to be implemented.

Hemisphere asymmetry

The issue of hemisphere asymmetry in face processing has already been alluded to earlier, and only the salient features of this issue will be discussed here. The main conclusion to be drawn from this study is that the contribution of the right hemisphere to face recognition appears to be both necessary and sufficient. The left hemisphere does participate in this function, but the operations which it implements are probably not specific nor essential to the processing of faces as such and only complement those carried out by the right hemisphere. In the present study, the participation of the left hemisphere involved the lateral occipito-temporal cortex, the fusiform gyrus which also contributed to the recognition of objects and the anterior temporal cortex. Whether the latter structure performs essential operations in face recognition cannot be determined from this study, but the findings of Ellis *et al.* (1989) showing a loss of evocation of personal information after damage of the right anterior temporal cortex may indicate that the left temporal cortex is not sufficient on its own to reactivate the pertinent records of personal information.

There are, however, a series of findings suggesting that the left hemisphere is not a silent partner in the processing of faces. For instance, both disconnected hemispheres of commissurotomized patients can identify faces (Levy *et al.*, 1972; Sergent, 1990). Moreover, a large number of divided visual-field studies in normal subjects have shown that initial stimulations of the left hemisphere may result in more accurate and faster recognition of faces than initial stimulations of the right hemisphere (e.g. Marzi and Berlucchi, 1977; Sergent, 1985, 1989). The present study was designed to examine this contradiction further by conducting a divided visual-field study on the subjects who had participated in the PET study, and the results provide some clues as to its origin. When considering the overall results of the lateral face-identity condition, a significant left-hemisphere advantage obtained, which would be interpreted as an indication of a superiority, if not a specialization, of the left hemisphere in the processing of faces, in contradiction with the results of PET study performed on the same subjects. However, when considering only the first lateral presentation of each face, a right-hemisphere advantage prevailed, in accordance with the findings of the PET study. This illustrates a methodological problem associated with typical divided visual-field studies that usually involve a relatively small number of faces, with which subjects are familiarized before the experiment, which are repeatedly presented during the test session, always under the same format (e.g. Sergent, 1985). Such conditions do not correspond to those prevailing in our normal dealings with faces and, as noted earlier, when right-hemisphere injured prosopagnosics are subjected to experimental conditions such as these, they are able to learn and recognize faces after a large number of trials and with the same version of faces, but they fail if a different version of the faces is later presented. This suggests that the capacity of the left hemisphere to process faces, and its apparent superiority in some divided visual-field studies with normals, can be demonstrated in artificial conditions that have little in common with natural situations; nonetheless, this also suggests that the left hemisphere can learn to process faces in some conditions and can thus assist the right hemisphere and implement some operations the contribution of which is not negligible even if it is not indispensable.

Conclusions

The present PET study is the first to examine face identification in comparison with object recognition. The results illustrate the contribution of the PET technique to a better understanding of the relationships between cognitive functions and cerebral structures, as well as the limits of this technique. A pessimistic evaluation would consist in suggesting that we do not learn, out of the PET data, more than we already knew about the anatomical substrates of face processing. Although there is some truth in such an assertion, it would not be fair. In using a new technique, one must first demonstrate its validity, which can be achieved only by confronting its results with those obtained through other, well-established procedures such as the anatomo-clinical approach. In this respect, the present results offer a clear demonstration of the validity of the PET technique, as the main findings are consistent with the evidence from neurological patients (*see* Damasio *et al.*, 1990*a*). Thus, once the validity and potential of this technique is demonstrated, it becomes possible to undertake experiments which are inaccessible to the anatomo-clinical approach, with the guarantee that the technique produces reliable findings. In addition, the visualization of activated cerebral areas in *normal* subjects provides information about the functional neuroanatomy of a given function that is not influenced by secondary effects of a lesion while making it possible to understand such effects better by comparing anatomical data in normal and brain-damaged subjects.

The benefits associated with the PET approach to the study of brain-behaviour relationships should not mask its inherent limitations nor the risk to promote a modern type of phrenology that would disregard evidence of interactive and distributed processing carried out in cerebral structures. One major limitation of the PET technique derives from the static and cumulative nature of the data it produces, which conceals the temporal and relational components of cerebral information processing. For instance, in the present data, it cannot be determined whether the involvement of a cortical structure (e.g. the left fusiform gyrus in the face-identification task) is conditional to earlier operations in another structure (e.g. the right lingual and fusiform gyri). In addition, in the subtraction method, it is assumed that the inclusion of a new cognitive operation to a given task does not affect the operations taking place at stages prior to this new operation, otherwise the subtraction of activation levels of two tasks would not be justified. Yet, this assumption may not be valid given the parallel processing of information in the brain and the retroactivation resulting from processes on earlier operations which, logically and theoretically, precede them but the functioning and organization of which are not necessarily governed by the same logic that guides our way of conceiving them. The results of PET measurements need to be confronted with findings from other sources, but, even if this technique is not self-sufficient, it provides a significant contribution to the multidisciplinary and asymptotic approach to the understanding of brain-behaviour relationships.

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NEGLECT OF NEAR PERIPERSONAL SPACE

EVIDENCE FOR MULTIDIRECTIONAL ATTENTIONAL SYSTEMS IN HUMANS

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SUMMARY

Neglect is most commonly observed and studied in the horizontal spatial dimension. Vertical neglect has been described in a few studies. We now report on a patient with near radial space neglect following bilateral posterior parietal lobe lesions Our patient also had neglect of inferior vertical and left horizontal space. These spatial deficits appear primarily attentional. Our findings compliment other studies that demonstrate neglect may occur in multiple spatial dimensions and provide evidence for a three-dimensional attentional system in humans. Whereas neglect of inferior vertical space may be associated with bilateral parietal lobe lesions, neglect of superior vertical and far radial space has been associated with bilateral inferior temporo-occipital lesions.

INTRODUCTION

Spatial neglect refers to a patient's unawareness and/or a failure to act on certain aspects of the environment. Patients who manifest neglect fail to report, respond or orient to stimuli in specific locations of space (Heilman *et al.*, 1985). Neglect following unilateral brain lesions is typically demonstrated in the hemispace contralateral to the lesion (for reviews, *see* Weinstein and Friedland, 1977; Jeannerod, 1987). Right-sided lesions produce left hemispatial neglect, and left lesions produce a neglect of right hemispace. The consistency of such phenomena has led to a view of the brain, and ultimately the control of human behaviour, as right-left hemispacially organized (Heilman *et al.*, 1990).

Recent investigations in humans (Rapcsak *et al.*, 1988; Shelton *et al.*, 1990), however, have revealed that attentional mechanisms may be more complex than a simple right-left dichotomy. Attention may be oriented in three dimensions of space: horizontal, vertical and radial; and the mechanisms mediating these attentional dimensions may be anatomically localized, as is the case for right-left hemispatial attention (Heilman *et al.*, 1983). For example, patients with neglect often omit more cancellation test items in the lower than upper quadrants of a radially aligned page (Morris *et al.*, 1985; Halligan and Marshall, 1989). Also, patients with unilateral left neglect have been shown to misbisect vertically presented lines above their midpoint (Bender and Teuber, 1948) and radially oriented lines beyond the centre (Marshall and Halligan, 1990). Theories concerning the left-right distribution of attention cannot fully explain inattention in near

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radial and lower vertical dimensions. Rapcsak *et al.* (1988) reported a patient with bilateral parieto-occipital infarctions and Balint's syndrome, who consistently misbisected vertical rods above their true midpoint. These misbisections were multimodal, occurring in both visual and tactile bisection tasks. Additionally, their patient extinguished stimuli presented in the lower visual fields during double simultaneous stimulation. Such inattention to stimuli arrayed in vertical dimensions was referred to as altitudinal neglect.

Shelton *et al.*'s (1990) patient with bilateral temporo-occipital lesions misbisected vertical lines significantly below their true midpoint and had extinction to stimuli presented in the upper visual quadrants as well as neglect for the upper portions of figures and drawings. Thus, he represented a form of altitudinal neglect opposite to that reported by Rapcsak *et al.* (1988), which was secondary to inferiorly localized lesions. In addition, Shelton *et al.* (1990) examined neglect for visual and tactile stimuli presented radially and found that their patient consistently misbisected radial lines toward his body.

Since Shelton's patient demonstrated neglect for upper visual and far peripersonal space following bilateral lesions of the temporo-occipital junction, it may be that structures located inferiorly in the brain are important for attending to superior and far spatial dimensions. Conversely, given the results of the patient of Rapcsak *et al.* (1988), certain parieto-occipital areas may support attention for inferior spacial dimensions. We do not know, however, if the same parieto-occipital areas play a role in monitoring near peripersonal space since radial neglect was not assessed in the Rapcsak *et al.* (1988) study.

This study re-examined the patient of Rapcsak *et al.* (1988) using the paradigm of Shelton *et al.* (1990). If the systems important for attending to upper vertical space are also involved in monitoring far peripersonal dimensions, then systems that monitor lower vertical space may also monitor near peripersonal dimensions. We would, therefore, predict an opposite pattern of findings for the patient in the study of Rapcsak *et al.* (1988) than for the patient in the study of Shelton *et al.* (1990). Specifically, the patient with bilateral parietal lesions should neglect near peripersonal space in addition to neglect of inferior vertical dimensions.

EXPERIMENT ONE

Subjects

The patient tested in this study was first investigated by Rapcsak *et al.* (1988). The following summarizes relevant findings from the earlier report and presents more recent evaluations. At age 41 yrs, this left-handed hypertensive women developed a sudden bilateral visual loss. Her vision improved over several days but she complained of occasional inabilities to see the lower half of fixated objects. Foveated objects sometimes faded from awareness. She could detect stimuli in all quadrants of the visual field, but extinguished stimuli in the lower quadrants to doubled simultaneous stimulation. Her perceptual deficits were characteristic of simultanagnosia and she had a severe impairment of voluntary eye movements in both horizontal and vertical directions. Her saccades were inaccurate, over or undershooting targets, and pursuit movements were often interrupted by saccades. Optic ataxia was pronounced. Reading was also severely impaired as her ability to attend to letters and move her eyes accordingly was severely compromised. She showed evidence of impairment in mental spatial representations as well. She could not visualize the layout of rooms or describe familiar spatial routes and her horizontal line bisections were shifted to the right of midline.

MRI performed 10 days after admission showed bilateral lesions, including the left angular gyrus (Brodmann's area 39), lateral occipital gyrus (Brodmann's area 19), inferior angular gyrus (Brodmann's area 39), posterior portion of the right middle temporal gyrus (Brodmann's area 37) and the lateral occipital gyrus (Brodmann's area 19). Although adjacent white matter was involved, the thalamus and basal ganglia were bilaterally spared (*see* Rapcsak *et al.*, 1988).

Controls

Control data were obtained from the study of Shelton *et al.* (1990), which included eight patients selected from Orthopaedics and Internal Medicine Services who were screened for neurologic and psychiatric diseases. Their mean age was 57 yrs, and their mean educational level was 10 yrs. Four healthy volunteers also participated (mean age = 35 yrs), which resulted in a combined total of eight males and four females.

Apparatus and procedures

Materials, procedures and methods followed the study of Shelton *et al.* (1990). However, whereas Shelton *et al.* obtained tactile rod bisections in only four locations, we obtained similar data in six locations. We also performed a second experiment designed to separate the influences of attentional and intentional mechanisms in line bisection tasks.

Visual bisection. The patient bisected black lines, 2.5 mm in width and of varying lengths (i.e. 20, 22, 24, 26, 28 and 30 cm), in three axial conditions: horizontal, radial and vertical Both hands were used to perform the bisections in an alternating fashion. Horizontal line bisections, in the transverse plane, were completed on a table top approximately 30 cm in front of the patient. There were three locations along a horizontal axis on which the midpoint of a line was placed before bisection: (1) 30 cm to the right of midline; (2) at midline; and (3) 30 cm to the left of midline. Radial line bisections were also completed on a table top along an axis that radiated out in one direction corresponding to the patient's midsagittal plane. Three placement locations were used in this condition corresponding to near (paper adjacent to patient's body), middle (30 cm from patient's body) and far (60 cm from patient's body) peripersonal space. Vertical lines (in the coronal plane) were presented on a door approximately 30 cm in front of the patient. There were six locations alone a midsagittal vertical axis on which the midpoint of lines or rods were placed before bisection (i.e. eye level, 15 cm above eye level, and 15, 30, 45 and 60 cm below eye level).

Tactile bisections. Wooden dowels 2.5 mm in diameter and of varying lengths (20, 22, 24, 26, 28 and 30 cm) were the stimuli for this task. The subject was blindfolded and asked to bisect rods after palpating their entire surface. Again, both hands were used in an alternating fashion. At the start of each trial, the subject's finger was placed on one end of the rod. Finger placement alternated between trials corresponding to a counterbalanced schedule. Rods were fixed to cards so they could be aligned along the same axes as in the visual bisections.

The patient received two blocks of six trials (two trials per line length) in each position of each axial condition. Trials were randomly administered across the placement locations within a given axial condition until all blocks were completed. A total of 288 line bisections were completed over the course of the day with breaks between the blocks of trials.

Controls received fewer trials, only one block per six locations, in the visual bisection task (i.e. left and right horizontal, near and far radial, eye level and 30 cm below eye level vertical conditions). Controls bisected rods in four locations of the tactile bisection condition (i.e. near and far radial, eye level and 30 cm below eye level vertical).

Analysis

Two dependent variables were of interest in this study: line bisection error (LBE) and the size of error in proportion to the line length. Line bisection error was the length of the segment between the actual midpoint of the line and the perceived midpoint defined by the subject's bisection. Line bisection error was recorded in centimetres with an error of approximately ±0.1. Proportional scores were simply the LBE divided by the line length. Bruyer (1984) showed that to make meaningful statements about the interaction between neglect and changes in the line length during bisection tasks one must consider proportional errors.

Direction of line bisection errors are shown in the respective table of means for visual and tactile line bisections (i.e. Tables 1 and 2). Positive numbers denote bisections to the right of the midpoint in horizontal conditions, away from the subject in radial conditions, and above the true midpoint in vertical conditions. To judge whether our patient's LBEs were significantly different from those of controls, 95% confidence intervals were set for LBE scores of the normals according to the procedures for small samples (Ferguson, 1966), where t values ($P < 0.05$, two-tailed test) are used to fix limits of 95% intervals according to

TABLE 1 TABLE OF MEANS, SDs AND PROPORTIONAL ERRORS FOR VISUAL LINE BISECTIONS

A Horizontal LBEs

	Left			*Centre*			*Right*		
Line length	*Mean*	*(SD)*	*Proport. error*	*Mean*	*(SD)*	*Proport. error*	*Mean*	*(SD)*	*Proport. error*
20	3.9	(0.42)	0.195	2 95	(0.77)	0 147	4.7	(0 77)	0.207
22	4.4	(0.14)	0 20	4.7	(0.84)	0.213	4.4	(0.42)	0.20
24	4 4	(0 56)	0 183	4.45	(0 63)	0.185	5 15	(0 35)	0.21
26	4.35	(0 07)	0 167	5.0	(0.42)	0.192	5.25	(0.77)	0 20
28	6 45	(0.21)	0.23	7.0	(1 2)	0.25	5.4	(0.98)	0.19
30	5.8	(0 98)	-0 193	6 05	(1.06)	0.20	6.7	(0.86)	0.22
Overall	4.88	(1.02)	0.195	5.02	(1.47)	0.20	5.17	(0.99)	0.206

B Radial LBEs

	Near			*Centre*			*Far*		
Line length	*Mean*	*(SD)*	*Proport. error*	*Mean*	*(SD)*	*Proport. error*	*Mean*	*(SD)*	*Proport error*
20	0 20	(6.08)	0.01	6.3	(0.14)	0 315	7.0	(0.28)	0.35
22	−0.25	(5.0)	−0.001	−0 01	(9 8)	−0.004	8 8	(0.70)	0.4
24	1 0	(10 4)	0.03	6.25	(2.7)	0 26	7.7	(0.56)	0.32
26	6 5	(0.98)	0.25	10 05	(0.35)	0.38	7.9	(1.6)	0.30
28	10.5	(0 77)	0.37	10.2	(0.9)	0 36	9.0	(0.98)	0.32
30	11.3	(0.98)	0.19	10 9	(1 13)	0 36	10.25	(2 19)	0.34
Overall	4 88	(6 5)	0.19	7 27	(5.04)	0.29	8 45	(1.42)	0.33
Adj overall	8.2	(2.96)	0.28	8 58	(2.33)	0.34			

C. Vertical LBEs

	+15 cm			*Eye level*			*−15 cm*			*−30 cm*			*−45 cm*			*−60 cm*		
Line length	*Mean*	*(SD)*	*Proport error*	*Mean*	*(SD)*	*Proport. error*	*Mean*	*(SD)*	*Proport. error*	*Mean*	*(SD)*	*Proport. error*	*Mean*	*(SD)*	*Proport error*	*Mean*	*(SD)*	*Proport error*
20	7 65	(0.91)	0.38	7.4	(0.28)	0 37	7.35	(1 06)	0 36	7.7	(0)	0.38	6 7	(1.41)	0 33	8 6	(0.28)	0.43
22	8.0	(0.42)	0.36	7 85	(0.07)	0.35	8.05	(0.21)	0.36	8.05	(0.63)	0.36	8.6	(1 69)	0 39	8.75	(0.91)	0.39
24	10.1	(0.14)	0.42	9.95	(1.06)	0 41	8.35	(0.91)	0.34	9 85	(0 77)	0.41	9.0	(0.42)	0.37	9 8	(0.28)	0.40
26	9.75	(0.21)	0.37	10.1	(0.07)	0.39	8.65	(2.1)	0.33	9.95	(0.35)	0.38	8 3	(1.13)	0.31	10.1	(0.28)	0 36
28	10 9	(0.21)	0.39	11 8	(0.56)	0.42	10.3	(1.5)	0.36	10.2	(1.13)	0.36	11.2	(0.14)	0.4	11 0	(0.42)	0.39
30	11.8	(0 70)	0 39	11.8	(0 56)	0.39	12 3	(0.77)	0 41	11 9	(0.84)	0.39	11.4	(0.14)	0 38	11.0	(0.42)	0 36
Overall	9 7	(1 5)	0 38	9.82	(1 84)	0.39	9.17	(1.99)	0 36	9.6	(1.56)	0 38	9 2	(1 88)	0.36	9.87	(1 06)	0.39

TABLE 2. TABLES OF MEANS, SDs AND PORPORTIONAL ERRORS FOR TACTILE LINE BISECTIONS

A. Horizontal LBEs

	Left			*Right*		
Line length	*Mean*	*(SDs)*	*Proport. error*	*Mean*	*(SDs)*	*Proport. error*
20	4.6	(1.7)	0.23	1.6	(1.5)	0.08
22	1.4	(1.6)	0.06	4.95	(1.2)	0.22
24	3.95	(0.07)	0.16	3.95	(0.49)	0.16
26	4.75	(1.76)	0.18	5.07	(0.91)	0.195
28	2.5	(0.56)	0.08	3.15	(1.2)	0.112
30	6.4	(1.27)	0.21	2.3	(2.6)	0.07
Overall	3.93	(1.7)	0.157	3.5	(1.4)	0.14

B. Radial LBEs

	Near			*Far*		
Line length	*Mean*	*(SDs)*	*Proport. error*	*Mean*	*(SDs)*	*Proport. error*
20	2.4	(1.27)	0.12	3.1	(0)	0.05
22	1.87	(1.95)	0.08	1.2	(1.6)	0.05
24	4.35	(0.77)	0.18	1.35	(1.34)	0.05
26	3.8	(0.42)	0.14	3.15	(0.07)	0.12
28	3.5	(0.7)	0.125	2.2	(0.42)	0.07
30	5.6	(0.7)	0.187	3.95	(1.06)	0.13
Overall	3.58	(0.7)	0.187	2.49	(1.09)	0.09

C. Vertical LBEs

	Eye level			*−30 cms*		
Line length	*Mean*	*(SDs)*	*Proport. error*	*Mean*	*(SDs)*	*Proport. error*
20	2.3	(0)	0.115	2.45	(0.35)	0.122
22	2.6	(1.13)	0.12	2.65	(0.21)	0.12
24	5.0	(2.8)	0.21	3.35	(0.63)	0.13
26	1.6	(1.13)	0.06	4.65	(0.91)	0.17
28	4.2	(0.7)	0.13	4.75	(0.63)	0.16
30	4.0	(1.27)	0.13	4.05	(2.6)	0.135
Overall	3.28	(1.3)	0.13	3.65	(0.98)	0.141

the degrees of freedom. Nonparametric statistics for correlated samples were then used to evaluate the patient data. Friedman's Rank Test (FRT) for correlated samples (a nonparametric analogue of repeated measures ANOVA) and the Wilcoxon matched-pairs signed-ranks test (a distribution free analogue of the *t* test for matched pairs) were used to analyse experimental effects

Results

Our patient clearly showed a consistent directional preference in visual line bisections (*see* Table 1). She bisected horizontal lines to the right of midline, radial lines away from peripersonal space and vertical lines above the actual midpoint. In fact, only three deviations from this pattern occurred (less than 2% of trials). All deviations were confined to near and centre placements along the radial axis. For purposes of comparison then, Table 1 also lists the overall adjusted means for these two conditions when the aberrant scores were excluded.

The patient misbisected lines to a significantly greater degree than controls. Her mean LBE scores were consistently outside the 95% confidence intervals set by controls in all axial conditions (*see* Table 3). Further, the magnitude of this difference was great as is clearly demonstrated by expressing the patient's LBE scores as *z* scores for controls. All conversions resulted in a *z* score of 6.4 or greater. The hand used to bisect lines did not significantly alter either the size or direction of line bisection error, so the data for both hands were pooled.

TABLE 3 TABLE OF MEANS, SDs AND PROPORTIONAL ERRORS FOR VISUAL AND TACTILE BISECTIONS OF 12 CONTROL SUBJECTS*

A. Visual LBEs

Placement	*Mean*	*(SD)*	*Proport. error*	*(Confidence intervals)*
Near	0.65	(0.66)	0.026	0.23−1.06
Far	0.90	(0.66)	0.036	0.48−1.32
Eye level	0.75	(0.42)	0.03	0.48−1.01
Below	0.54	(0.40)	0.021	0.19−0.88

B. Tactile LBEs

Placement	*Mean*	*(SD)*	*Proport. error*	*(Confidence intervals)*
Near	−0.09	(0.68)	0.003	−0.52−0.34
Far	−0.92	(0.99)	0.037	−1.54−−0.29
Eye level	−0.34	(1.42)	0.014	−1.24−0.56
Below	−0.38	(1.11)	0.015	−1.08−0.32

*Data taken from Shelton *et al.* (1990). Horizontal LBEs were not significantly different from 0, therefore means were not reported. d.f. = 11 (n−1) $P < 0.05$ two tailed

Placement of stimuli within horizontal, radial or vertical conditions did not have a significant effect on the LBE scores. No significant hemispace effect emerged in the horizontal (i.e. left vs middle vs right) ($\chi^2 = 3.25$, d.f. = 2, NS) radial (i.e. near vs far) ($\chi^2 = 1.83$, d.f. = 2, NS), or vertical (superior vs inferior) conditions ($\chi^2 = 4.19$, d.f. = 5, NS).

Changing the line length did have a significant effect on LBE scores in the vertical condition, but this effect faded when proportional scores were examined. Examining the effect of line length across each axial condition revealed no significant change in LBE scores for either of the horizontal ($\chi^2 = 8.19$, d.f. = 5, NS) or radial ($\chi^2 = 6.93$, d.f. = 5, NS) conditions. However, in the vertical condition LBE increased as the length of the line became greater ($\chi^2 = 28.1$, d.f. = 5, $P < 0.005$), but this significant effect could not be replicated when proportional scores were entered in place of LBE values ($\chi^2 = 9.97$, d.f. = 5, NS). Rather, the patient consistently neglected about 37.6% of the line no matter what its length.

The patient's data were also analysed to determine whether LBEs differed across horizontal, radial or vertical conditions. Friedman's Rank Test revealed a significant effect of axial condition ($\chi^2 = 10.3$, d.f. = 2, $P < 0.01$). Mean LBEs in the vertical condition were significantly larger than those in either the horizontal (T = 0, n = 6, $P < 0.015$) or radial (T = 0, n = 6, $P < 0.015$) conditions. The latter two conditions did not differ significantly from each other (T = 3, n = 6, NS).

The next analyses examined data in the tactile bisection condition. Table 2 gives the means, standard deviations and proportional values for tactile LBEs. First, the direction of tactile LBEs in the tactile line bisection were identical to those in the visual condition. Horizontal lines were consistently bisected to the right of the true midpoint, radial lines were bisected away from the subject, beyond the true midpoint, and vertical lines were bisected above the true midpoint. Secondly, tactile LBEs were not only significantly larger than those for controls, but also opposite in direction (*see* Table 4). Mean LBEs for the patient were consistently outside the 95% confidence intervals established by controls. Expressing the patient's LBEs as z scores for the controls further exemplifies the significant difference. All z scores were greater than 2.5.

The Wilcoxon test was used to examine the effect of stimuli placement within axial condition. As for the visual bisections, no significant effects of stimuli placement were detected (i.e. horizontal condition: T = 10, n = 6, NS; radial condition: T = 3, n = 6, NS; vertical condition: T = 16, n = 6, NS). Also, changes in rod length did not significantly effect the size of LBEs in either horizontal ($\chi^2 = 3.71$, d.f. = 5, NS), radial ($\chi^2 = 8$, d.f. = 5, NS) or vertical ($\chi^2 = 6$, d.f. = 5, NS) conditions.

Changes in the LBEs were associated with axial condition. Friedman's Rank Test revealed a significant effect of axial condition across horizontal, radial and vertical LBE scores (χ^2, d.f. = 2, $P < 0.025$). Mildly smaller LBE scores were observed in the radial rather than the horizontal or vertical conditions. Comparison of the LBE scores observed in the radial condition to LBEs averaged across horizontal and vertical conditions revealed a significant difference at the one-tailed level (T = 2, n = 6, $P < 0.0469$).

This effect must be considered marginal, however, because our real interest is at the two-tailed level of significance ($P < 0.075$).

Finally, modality effects (i.e. visual vs tactile bisections) were examined. Line bisections were significantly worse in all visual rather than tactile conditions. When averages for the visual horizontal condition were compared with those for the tactile horizontal condition, a significant modality effect was revealed ($T = 1$, $n = 6$, $P < 0.031$). Likewise, modality effects were obtained for the radial ($T = 0$, $n = 6$, $P < 0.015$) and vertical conditions ($T = 0$, $n = 6$, $P < 0.015$)

Discussion

Bilateral parieto-occipital lesions, in our case, caused a pattern of neglect opposite that of a previously reported case with bilateral inferior temporo-occipital infarctions (Shelton *et al.*, 1990). Although the patient of Shelton *et al.* (1990) bisected vertical lines below their true midpoint and radial lines toward near peripersonal space, the patient of Rapcsak *et al.* (1988) bisected vertical lines above the midpoint and radial lines away from near peripersonal space. These effects were observed in both visual and tactile line bisections.

Neglect was significantly worse in the visual rather than the tactile modality. On the average, visual LBEs were two times greater than tactile LBEs. This finding is consistent with that of the patient of Shelton *et al.* (1990). However, the current pattern is different from the original study and 3 mth follow-up of Rapcsak *et al.* (1988). They recorded an average error of 6.86 cm for visual and 6.57 cm for tactually bisected lines, and our mean error scores were 9.56 cm and 3.65 cm, respectively. Rapscak *et al.* (1988) alternated among visual, tactile and visual-tactile bisections in successive trials. We tested the patient in non-overlapping blocks (i.e. either all visual or tactile-proprioceptive). Therefore, the difference may be due to methodology. However, these results may also reflect changes in the patient since we tested her 3 yrs after the stroke.

Within the visual mode, LBEs were greatest in the vertical dimension (9.56 cm vertical vs 5.02 cm horizontal vs 6.86 cm radial). Differences among axial conditions in the tactile bisections were not great (3.65 vs 3.82 vs 3.12). These findings suggest that brain lesions may cause differential effects not only between modalities but also across spatial dimensions within a modality. Attention in humans may thus be fractionated by both modality and spatial dimension. These fractionations are consistent with observations following surgical ablations in primates (Rizzolatti *et al.*, 1983) and in patients with head trauma (Butter *et al.*, 1989).

EXPERIMENT TWO

Watson *et al.* (1978) make a distinction between attention and intention mechanisms in neglect. Attentional processes are most important in building stimulus representations, but intentional mechanisms refer to the preparatory stages of a movement. Whereas failures of the attentional systems induce unawareness, failure of the intentional systems induce inaction. A precise separation of these components is hard to achieve but their existence in humans has been suggested in line bisection experiments that varied the mode of input and/or output for a given task. Two recent studies have used innovative ways of separating either the hemispace of sensory input from motor output (Coslett *et al.*, 1990) or 'perceptual' from 'premotor' influences on line bisection tasks (Bisiach *et al.*, 1990) in neglect. In both studies subjects' performances could be roughly divided into those more influenced by attentional (perceptual) or intentional (premotor) mechanisms. There was a tendency for patients with a greater degree of frontal lobe involvement to be relatively more affected by intentional influences in line bisection tasks (Bisiach *et al.*, 1990; Coslett *et al.*, 1990) but this relationship is not absolute. Intentional deficits have also been produced by parietal lobe lesions in monkeys (Valenstein *et al.*, 1982).

Our second experiment investigated motor intention in line bisection tasks.

Apparatus and procedures

Three conditions were used to control the degree and type of motor response required for the line bisection task. In the 'motor-free' condition, the patient watched a mechanical stylus move from either 'top to bottom' or 'bottom to top' along a radial line and then indicated verbally the subjective centre. The patient was free to adjust the stylus by directing the experimenter to move either up or down. Stylus speed was constant at approximately 2 cm per second.

Conditions requiring motor movements were labelled either congruent or incongruent depending on the direction of the motor response in relation to the movement of the stylus. During 'congruent' motor trials the patient bisected lines directly by moving the stylus with her hand. As above, the patient began at either the top or bottom of the line according to a counterbalanced schedule. 'Motor incongruent' trials required the patient to move her hand in the opposite direction of the stylus. She controlled the movement of the stylus by manipulating an attached string that was looped around pulleys. To move the stylus one direction (e.g. up) she had to pull the string in the opposite direction (i.e. down). The same apparatus was used in all conditions. It was similar to one described by Bisiach *et al.* (1990) consisting of a 30×20 cm platform with pulleys attached to each end. A string belt surrounded the pulleys and held the stylus over the platform's surface. Sheets of paper printed with 2.5 mm lines of varying lengths (20, 22, 24, 26, 28 and 30 cm) were inserted between the stylus and the platform's surface. The patient's bisection performance was recorded on the inserted page. During incongruent motor trials the platform was suspended over the table top so the stylus could be moved by use of the string beneath the platform. Both hands were used in an alternating fashion. Shields prevented the patient from observing her own arm and hand movements during these trials.

All bisections were performed in either near or far radial conditions. Seventy-two trials were completed in six blocks. Twelve observations (two trials per line length) were obtained in six conditions: motor-free, motor congruent and motor incongruent (far) radial bisections, and free, congruent and incongruent (near) radial bisections. Line bisection error was the dependent variable

Analyses and results

Statistical methods for this experiment were identical to those in Experiment 1. As in Experiment 1, a consistent directional neglect was observed. The direction of bisection errors may be obtained from the table of means and standard deviations (Table 4). With only five exceptions (less than 7% of trials), lines were bisected beyond the midpoint, in the direction away from peripersonal space. As in Experiment 1, the exceptions occurred in the near radial condition. Lines were misbisected to a significantly greater degree than those obtained for controls in Experiment 1. The patient's LBE scores were consistently outside the 95% confidence intervals established for controls in both near and far radial conditions.

TABLE 4 TABLE OF MEANS, SDs AND PROPORTIONAL ERRORS FOR LINE BISECTIONS IN DIFFERENT MOTOR CONDITIONS

A. Far Radial LBEs

Line length cm	*Motor free*			*Motor congruent*			*Motor incongruent*		
	Mean	*(SD)*	*Proport. error*	*Mean*	*(SD)*	*Proport error*	*Mean*	*(SD)*	*Proport. error*
20	3 55	(0 63)	0.177	3 15	(0 157)	0 187	3 75	(1.34)	0 188
22	3.35	(0.07)	0 152	3.45	(0 156)	0 168	3 7	(0 42)	0.168
24	4.15	(0.35)	0.172	4.8	(0.20)	0.173	4.15	(0.63)	0.173
26	5 3	(0.98)	0.20	5 95	(0.228)	0.209	5 45	(0.35)	0.208
28	3.7	(3.39)	0.13	4.05	(0.144)	0.20	5.85	(0.49)	0.208
30	7 5	(0 14)	0.25	6.35	(0 21)	0.19	5 8	(0.28)	0.193
Overall	4.59	(1.86)	0.184	4 62	(1.58)	0.185	4 78	(1.10)	0 191

B Near Radial LBEs

Line length cm	*Motor free*			*Motor congruent*			*Motor incongruent*		
	Mean	*(SD)*	*Proport. error*	*Mean*	*(SD)*	*Proport error*	*Mean*	*(SD)*	*Proport. error*
20	2.8	(0 42)	0.14	2 4	(0.56)	0.12	3 55	(0.6)	0.177
22	1 2	(2.68)	0.05	3 2	(0 28)	0 145	3 25	(1.9)	0.147
24	1.15	(2.1)	0.04	3.7	(0.98)	0.142	4.5	(0 42)	0 187
26	4.55	(1.6)	0.175	5.65	(0.21)	0.217	1 55	(2 19)	0 06
28	4 75	(0 07)	0 169	1.0	(5 0)	0.03	1.6	(2.2)	0.057
30	3.0	(1.5)	0.10	4.9	(2.4)	0.163	4 15	(1 48)	0.138
Overall	2.91	(1.98)	0.116	3.46	(2 36)	0 138	3 1	(2 64)	0 124

Manipulating motor involvement (i.e. congruent and incongruent and motor free) did not lead to significant changes in LBE scores for either far ($\chi^2 = 1.75$, d.f. = 2, NS) or near ($\chi^2 = 3$, d.f. = 2, NS) radial conditions. Similarly, line length had no effect on LBE scores in the near or far radial conditions when proportional scores were entered in place of LBE scores ($\chi^2 = 10.2$, d.f. = 5, NS). Line bisection errors were greater in the far than in the near radial condition ($T = 0$, $n = 6$, $P < 0.015$). The mean LBE in the far radial condition was 4.58 (1.5) cm compared with 3.22 (2.2) cm in the near radial condition. Further, proportional differences were significant ($T = 0$, $n = 6$, $P < 0.015$) suggesting our patient neglected a significantly greater proportion of the line in far radial space (18.3%) than near radial space (12.8%).

Finally, the last analysis drew comparisons between Experiments 1 and 2. Line bisection errors in the far radial conditions of Experiment 2 were intermediate to the LBEs obtained for visual and tactile radial bisections of Experiment 1 A series of analyses using the Wilcoxon test indicated that far radial LBEs in Experiment 2 (collapsed across levels of motor involvement) were significantly smaller than the visual far radial LBEs in Experiment 1 ($T = 0$, $n = 6$, $P < 0.013$). Respective means for the two conditions were 4.58 cm and 8.45 cm. Conversely, the far radial LBEs in Experiment 2 were significantly greater than tactile far radial bisections in Experiment 1 ($T = 0$, $n = 6$, $P < 0.013$). Means for these conditions were 4.58 and 2.49, respectively. No significant differences were found for similar comparisons in the near radial bisections of Experiments 1 and 2, owing largely to the increased variability observed in these data.

Discussion

Because our manipulation of motor involvement failed to produce a significant effect on the LBE scores, either the neglect observed in Experiment 1 was due to attentional rather than intentional deficits or our paradigm was ineffective. Recent studies have indicated that frontal lesions may be more influential in producing intentional rather than attentional neglect (Bisiach *et al.*, 1990; Coslett *et al.*, 1990). Because our patient's lesions were in posterior parietal areas, the nature of her deficits may be more perceptual (attentional) than premotor (intentional).

GENERAL DISCUSSION

Bilateral parieto-occipital lesions in the patient of Rapcsak *et al.* (1988) were associated with both neglect of near (radial) and inferior (vertical) peripersonal space. The neglect demonstrated by this patient was multimodal (i.e. occurring in both visual and tactile line bisections), but was significantly more pronounced in the visual modality. Further, her deficits appeared to be attentional rather than motor intentional in nature.

The direction of neglect in our patient's line bisections was opposite that of the patient of Shelton *et al.* (1990), except in one respect. Unlike Shelton's patient and other patients with either horizontal (Heilman and Valenstein, 1979) or altitudinal (Butter *et al.*, 1989) neglect, when our patient performed radial bisections in the visual condition her neglect did not become worse as stimuli were placed farther within the neglected field. However, her radial bisections in the tactile condition deteriorated as they were performed in neglected space, suggesting that she may rely on different coordinate systems to perform the two tasks (i.e. visual and tactile bisections).

Stimuli may be spatially coded with regard to either egocentric (i.e. retinotopic, head centred-cephalocentric, and body centred-corpracentric) or environmental frames of reference (Marr, 1982; Coslett *et al.*, 1990; Farah *et al.*, 1990). These coding strategies may use separate systems, and these systems may be fractionated in brain-damaged individuals. Whereas visual bisections may rely heavily on retinotopic coordinates, tactile bisections may use predominantly body-centred coordinates. The patient of Rapcsak *et al.* (1988) may have problems visually coding the lower half of objects in addition to neglect of near space.

Line bisection errors in these studies suggest the existence of attentional mechanisms that are distributed along vertical and radial planes, just as errors in horizontal line bisection suggest the presence of hemispatial inattention along a horizontal plane (Bisiach and Vallar, 1988). Normal subjects also display subtle asymmetries in attention on line bisection tasks across horizontal (Bowers and Heilman, 1980; Bradshaw *et al.*, 1983; Scarisbrick *et al.*, 1987), vertical (Butter *et al.*, 1989; Shelton *et al.*, 1990) and radial (Shelton *et al.*, 1990) dimensions. Different experimental paradigms using normal subjects have also shown that attention can be directed along multiple spatial dimensions. Posner (1978) demonstrated that humans actively direct their attention in horizontal space. When stimuli fall within the boundaries of an expected attentional field, they enjoy a processing advantage. Subjects react faster to expected stimuli than to stimuli that fall outside their directed attentional field (unexpected). Similar costs in attentional shifting occur in vertical (Gawryszewski *et al.*, 1987; Hughes and Zimba, 1987) and radial (Downing and Pinker, 1985; Gawryszewski *et al.*, 1987) dimensions. These costs are greatest when subjects must shift attention from one hemispatial field to its opposite (Downing and Pinker, 1985; Hughes and Zimba, 1987) but within-field costs occur as well (McCormick and Klein, 1990). Whether the brain mechanisms controlling these shifts are antagonistic or parallel is not yet known. It seems clear, however, that the brain is specialized to monitor and shift attention along multiple spatial dimensions.

The areas of damage in the patients of Rapcsak *et al.* (1988) and Shelton *et al.* (1990) involved the parieto-occipital and inferior temporo-occipital cortex, respectively. Quite clearly, parietal neurons are involved in spatial coding. Steinmetz *et al.* (1987) showed that parietal visual neurons are important for projected arm and hand movements. Misreaching for objects in peripersonal space (optic ataxia) has been reported in both man (Balint, 1909) and monkeys (Humphrey, 1979) following damage of the posterior parietal cortex. Moreover, parietal neurons have attentional properties (Lynch *et al.*, 1977; Robinson *et al.*, 1978) and certain areas within the parietal lobes may be specialized for attending to near space. Leinonen *et al.* (1979) identified light-sensitive neurons in area 7B of monkeys that were only responsive to stimuli within peripersonal space, and Rizzolatti *et al.* (1985) showed that ablation of these neurons produced a neglect of near peripersonal space.

In contrast to the parietal cortex, inferior temporo-occipital areas have not been linked to neglect. These areas are important in the recognition, categorization and/or retrieval of shapes, colours, textures and objects (Penfield and Rasmussen, 1950; Mishkin, 1972; Sahgal and Iversen, 1978; Levine *et al.*, 1985). Further, they have been implicated in a system governing vision to far space (Previc, 1990). Infero-temporal lesions have been shown to disrupt attentional switching (Wilson *et al.*, 1972) and selection (Butter, 1968). However, other than the report of Shelton *et al.* (1990), the temporo-occipital areas have not been considered important in spatial attention. The dissociation between the patients of Shelton *et al.* (1990) and Rapscak *et al.* (1988) suggests that further investigation of the temporo-occipital areas is warranted.

The frontal lobes are also involved in the systems governing spatial attention. Rizzolatti *et al.* (1981) identified two sets of neurons in the periarcuate cortical region, anterior and posterior, that responded to far and near (within reaching distance) stimuli, respectively. The latter group could be further subdivided into bimodal neurons that responded to stimuli less than 10 cm from cutaneous receptors and those responsive to stimuli within, but not beyond, reaching distance. These neurons bear a striking resemblance to those identified in the parietal cortex (area 7B) by Leinonen *et al.* (1979). In fact, area 7B neurons project in a unidirectional fashion to the posterior periarcuate sulcus (Chavis and Pandya, 1976). Lesions of the frontal eye fields in monkeys lead to visual neglect of far space (Rizzolatti *et al.*, 1983). The frontal eye fields receive projections from area 7ip of the posterior parietal area (Barbas and Mesulam, 1981). Area 7ip receives afferents from a constellation of visual areas in both the temporal and occipital lobes (*see* Goldman-Rakic, 1987). Areas 7B and 7ip have relative, functional specializations, the former being activated more by somatosensory stimuli and the latter being responsive to visual stimuli, and may each be part of parallel systems that monitor near and far space.

Rizzolatti and Camarda (1987) have proposed that spatial attention is a modular function present in several independent circuits. Posterior parietal and frontal lobe connections appear to be organized as a set of parallel pathways that transmit specific types of information (Goldman-Rakic, 1987). Parietal areas, such as area 7ip, receive afferents from the occipital lobe, so it is conceivable that lesions in temporal-occipital cortex could disrupt the function of circuits important for monitoring far space. Additionally, it seems highly probable that bilateral lesions of the temporo-parietal junction could lead to neglect of near space. Our study and comparison with the patient of Shelton *et al.* (1990) supports recent evidence suggesting that attentional processes are mediated by independent neural circuits.

The patients of Rapcsak *et al.* (1988) and Shelton *et al.* (1990) are similar in that roughly symmetrical bilateral lesions were implicated. This observation raises some questions as to whether bilateral lesions are necessary to produce vertical or radial neglect. Could unilateral lesions produce a more subtle form of neglect in these dimensions? Some evidence may already exist to answer this question. Our laboratory and others (Morris *et al.*, 1985; Halligan and Marshall, 1989) have found that neglect on cancellation tasks is often worse in the lower contralateral quadrant of the page than any other. Cancellation tasks may confound two dimensions of space (i.e. right and left horizontal and near and far radial) because they are placed in front of the patient along a horizontal plane. Thus, in patients with unilateral lesions and neglect, omissions in contralateral hemispace could be due to the laterality of the lesion and omissions in near space could be due to lesions in areas responsible for attending to near space. Inferior parietal lobe lesions, or lesions occurring in systems that involve this area, most commonly produce neglect in humans (Heilman *et al.*, 1983), which may account for the greater omissions in inferior quadrants of cancellation tasks reported above. Neglect of inferior vertical (Bender and Teuber, 1948) and near radial (Marshall and Halligan, 1990) line lengths have also been reported following unilateral left brain lesions. After we submitted this paper for review, Halligan and Marshall (1991) submitted a study examining horizontal line bisection in near and far space. Neglect was either attenuated or abolished by placing lines in far space, suggesting further that near far neglect may be observed in patients with unilateral lesions.

Bilateral lesions may simply magnify vertical or radial neglect, making it apparent on line bisection tasks administered in these dimensions. Indirect evidence for this hypothesis comes from Bender's (1980) review of studies that delivered either unilateral or bilateral stimulation to the dorsal or ventral occipital lobes. Unilateral stimulation induced either upward or downward gaze movements but this effect was more pronounced, and thus clearer, with bilateral stimulation. In summary, there is reason to believe that subtle effects of vertical and radial neglect may be found following unilateral lesions.

The importance of the present case was in demonstrating neglect of near peripersonal space following bilateral parietal injury, which had not been investigated in Rapcsak's original study, and in providing further evidence of three-dimensional attentional systems in humans. We must caution, however, against generalizing from two case studies. Instead, our hope is that these findings will be validated by further research.

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NEGLECT AND VISUAL RECOGNITION

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SUMMARY

B.Q., a right-handed woman who had suffered a stroke affecting the right parietal region, showed visuospatial neglect and problems in recognizing seen objects and faces. Investigation of her visual recognition problems revealed a striking inability to identify the left sides of chimaeric objects and faces. Often, B.Q. would deny that the stimulus was chimaeric at all, and she was remarkably poor (though above chance) at discriminating chimaeric from normal faces. Even when left-sided details had been accurately traced or described, they were often either ignored in reporting the identities of the constituent parts of a chimaeric or assimilated in some way to the information from the right side.

Neglect of the left side was more pronounced for chimaerics which approximated an individual face or object. It occurred regardless of the chimaeric's position in B.Q's field of vision, and was found with brief (200 ms) presentations of stimuli confined to her (perimetrically intact) right visual field. When chimaeric faces were inverted, B.Q. continued to neglect the side of the chimaeric falling to her left, which implies that the neglect did not operate in entirely object-centred coordinates.

However, left-sided information could be used if it was critical in determining the identity of an object or a face. We suggest that this could explain B.Q.'s lack of neglect of individual words, for which left-sided (initial) letters are often crucial to successful recognition. An account of her deficit is proposed, involving an interaction between moderately defective pick-up of left-sided information in an object-based coding system and preserved access to stored representations of familiar visual stimuli.

INTRODUCTION

Unilateral neglect is often considered a disorder affecting attention to or the representation of space, but many of the observed phenomena relate to neglect of the left side of individual objects. For example, in drawing or copying, the left side of objects is often omitted (Heilman, 1979). In reading, the left side (initial letters) of words may be misread (Kinsbourne and Warrington, 1962; Ellis *et al.*, 1987).

For reading, there are grounds for thinking that omissions of words from the left side of the page and misreadings of the individual words themselves may have different underlying causes. Young *et al.* (1991) found that initial-letter misreadings could occur for words in any spatial location on the page, and even to tachistoscopic presentations confined to the right visual field. Even more remarkably, Costello and Warrington (1987) described a patient who misread the initial letters of words but showed right-sided neglect in other tasks.

The reading errors which arise in 'neglect dyslexia' have attracted a lot of interest (*see* Riddoch, 1990, 1991), but much less attention has been paid to neglect of other

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types of visual object. However, Humphreys and Riddoch (1991) have emphasized the theoretical importance of distinguishing object-based and spatially-based problems. Moreover, Gainotti *et al.* (1986) considered that neglect of one side of an otherwise attended stimulus may be the most characteristic feature of unilateral neglect resulting from right hemisphere lesions. Their findings showed that contralateral neglect could follow left or right brain injury in a task which required exploration of a relatively large area of space (searching for animals), whereas in a test involving the focusing of attention on small but complex stimuli (overlapping figures) only patients with right hemisphere lesions would neglect the contralateral side of each stimulus. Further studies of neglect of seen objects have been reported by Marshall and Halligan (1988), Kartsounis and Warrington (1989), Seron *et al.* (1989) and Bisiach and Rusconi (1990).

The present investigation sought further to explore the phenomenon of neglect of 'focally attended' stimuli reported by Gainotti *et al.* (1986) by investigating the object, face and word recognition abilities of a patient with a stable left-sided spatial neglect resulting from a right hemisphere stroke.

CASE DESCRIPTION

B.Q. was a right-handed retired professional woman, aged 64 yrs, who had suffered a stroke 5 mths previously. She was referred for further investigation because of her persistent unilateral neglect. She had left hemiplegia. Cranial nerves and fundi were normal, but there was left hemianopia with macular sparing on conventional perimetric testing. However, further investigation showed that B.Q. could report left visual field stimuli if the fixation point was removed before they were presented, leading us to question the appropriateness of hemianopia as a description of her visual field defect (Walker *et al.*, 1991).

CT scan showed an extensive low density region surrounding the right parietal region and moderate midline displacement. The neurological findings were considered to be consistent with an infarct in the territory of the right middle cerebral artery

No defects of speech or verbal comprehension were evident in conversation, but formal assessment gave a pro-rated verbal IQ of 97 (based on subtest scores: information, 10; arithmetic, 4; similarities, 12, vocabulary, 14), which was not consistent with her previous occupation or predicted premorbid IQ (127) using the NART (Nelson, 1982). There were no significant impairments of digit span (7 forwards, 4 backwards) or verbal recall (logical memory passages from the Wechsler Memory Scale: immediate 10, 10; after 40 min delay 10, 10).

In contrast to these well-preserved verbal abilities, visual copying and visual short-term memory showed obvious impairment. The block design subtest of the WAIS proved impossible for her. There was a marked left-sided neglect in letter cancellation tasks, in copying and drawing, and for line bisection with lines over 12.5 cm in length. In reading, B.Q omitted many words from the left side of the page.

INVESTIGATION AND RESULTS OF VISUAL RECOGNITION

Tests of B.Q.'s vision showed normal spatial contrast sensitivity function (using the Vistech Vision Contrast Test System chart) and normal acuity (N5). However, she was poor at recognizing pictures of objects, though by no means agnosic. She recognized 13/20 living objects (control mean = 18.30, SD = 1.06) and 15/20 non-living objects (control mean = 19.30, SD = 0.82) from the set used by Young and Ellis (1989).

Face processing abilities were also poor, with impaired recognition of familiar faces (14/20 correct; control mean = 18.86, SD = 1.15), impaired identification of emotional expressions (7/24 correct; control mean = 21.10, SD = 1.70), and impaired matching of unfamiliar faces (26/48 correct; control mean = 46.00, SD = 1.76).

In contrast, B.Q.'s reading of individual words was generally accurate. Although she tended to omit words from the left side of the page when reading, she made few misreadings of the words she did attempt. We will return later to consider B.Q.'s relatively well preserved recognition of individual words. First though, we examine in more detail her recognition of objects and faces.

Identification of half-stimuli and chimaerics

Because the use of half-stimuli and chimaerics had proved instructive in a previous case (Young *et al.*, 1990), a similar procedure was adopted with B.Q.

Photographs of approximately symmetric views of 10 everyday objects were separated at the vertical midline into left or right halves, with normal and mirror-reversed prints of these producing a set of 20 left half-objects and 20 right half-objects. To these were added 20 chimaeric objects, made by juxtaposing the left and right half-objects at random. Exactly the same stimuli were used as half-objects and in the chimaerics. The purpose of using 50% mirror-reversed prints was to control for the exact features which would appear in the left or right half-stimuli, and hence eliminate any influence of minor asymmetries in the objects themselves.

Figure 1 shows examples of the left and right half-objects, and the resulting chimaerics.

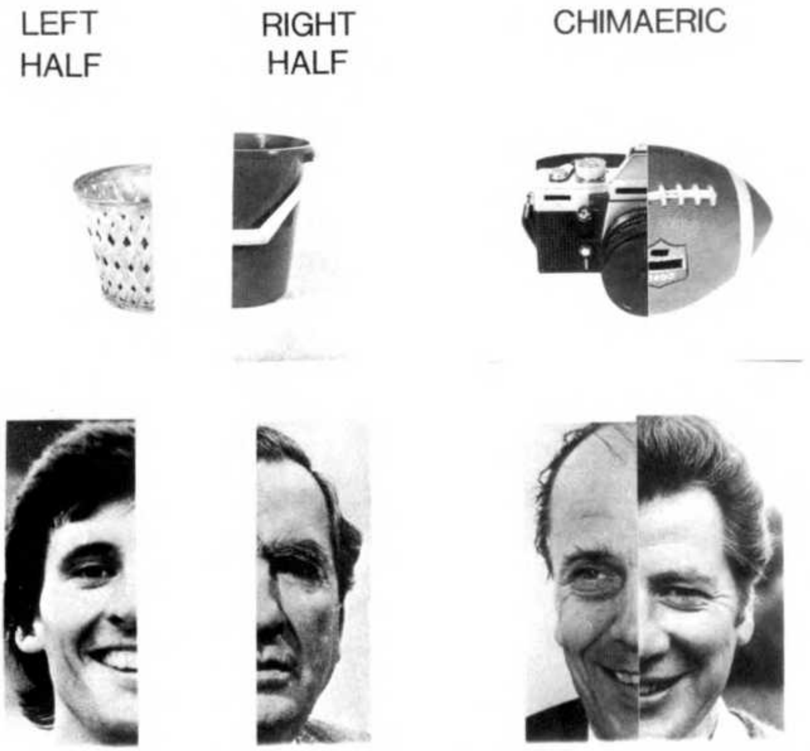


FIG. 1. Examples of left and right half-objects and half-faces, and chimaeric objects and chimaeric faces.

It is important to note that left and right sides are defined in terms of the side falling to B.Q.'s left or right.

A pre-test with photographs of each of the 10 objects was used to establish that B.Q. knew what each object was, and the 20 chimaeric objects, 20 left half-objects, and 20 right half-objects were then presented one at a time in random order. B.Q. was asked to identify each half-object, and both halves of the chimaeric objects. She was allowed to examine all of the stimuli for as long as she liked, and was reminded several times to try to identify both halves of the chimaerics.

An equivalent task using left and right halves of the faces of 10 famous people was also given to B.Q., and examples of the left half-face, right half-face and chimaeric faces are shown in Fig. 1. Again, our use of left and right refers to the side of the face falling to B.Q.'s left or right.

We will consider B.Q.'s performance in this and subsequent tasks in terms of the numbers of errors she made to the different types of stimulus. Results of the half-object and half-face tasks are presented as error rates in Table 1. B.Q. showed a marked problem in identifying the left side of chimaeric objects (errors on 14/20 trials with left sides, whereas she only made errors on 2/20 trials with right sides; two-tailed binomial $P < 0.005$) and chimaeric faces (errors on 20/20 trials with left sides, 0/20 trials with right sides; two-tailed binomial $P < 0.001$), whilst remaining much better able to recognize left half-objects (1/20 errors; comparison to error rate for left sides of chimaeric objects gives two-tailed binomial $P < 0.005$) or left half-faces (2/20 errors; comparison to error rate for left sides of chimaeric faces gives two-tailed binomial $P < 0.001$) presented in isolation. For many of the chimaerics, B.Q. did not even seem to notice differences between the left and right halves, and denied that anything other than the object or face on the right of the chimaeric was present. Hence it was not possible to control the order in which she was asked to report the left or right sides of the chimaerics, since for most of them she only reported the right side anyway. In fact, all of B.Q.'s 20 errors to the left side of chimaeric faces involved omissions, in which she reported the right side only; there were no cases in which she realized the stimulus was a chimaeric face but misidentified the left side. For the chimaeric objects, 13 of the 14 errors to the left sides were also of this type.

We are not claiming that B.Q.'s recognition of left or right half-stimuli was normal. The task is one in which we would expect normal subjects to be at ceiling, since correct recognition of all the objects and faces was established before each test with half-stimuli and chimaerics began. It may well therefore be the case that B.Q. did not recognize the left halves very well even when they were presented in isolation. Our main point,

TABLE 1

	Half-stimuli		*Chimaeric stimuli*	
	Left half	*Right half*	*Left side*	*Right side*
Objects	1/20	0/20	14/20	2/20
Faces	2/20	0/20	20/20	0/20

Error rates for B.Q.'s recognition of left and right half-objects and half-faces, and the left and right sides of chimaeric objects and faces.

however, is that B.Q. was much worse at recognizing left half-stimuli when they formed part of a chimaeric, and for this comparision she serves as her own control.

We do not think that there is anything remarkable about the fact that B.Q. could not recognize any of the left sides of the chimaeric faces (20/20 errors) whereas she did recognize some left sides of chimaeric objects (14/20 errors), since we made no attempt to control visual similarity of the stimuli in each category, and especially the extent to which the left and right sides of the chimaeric objects formed a good 'fit' alongside each other. The important point is that impaired ability to recognize the left sides of chimaerics was found for both classes of stimuli; B.Q.'s problem was not specific to faces.

This pattern is different from that shown by the previous case we described, K.L. (Young *et al.*, 1990). K.L. recognized the left and right sides of objects with equal ease, whereas he was impaired at recognizing the left half of faces both in chimaerics and when they were presented in isolation. We will return to consider the differences between K.L. and B.Q. later, when we have reported other tests designed to clarify the nature of B.Q.'s recognition impairment. A number of these tests used faces as convenient stimuli for which B.Q. had shown a pronounced impairment.

Orientation effects

The chimaeric faces were used to examine the effect of orientation on B.Q.'s ability to recognize left and right sides. Our intention was to explore whether viewer-centred or object-centred codes were compromised. If the problem affected viewer-centred codes, inversion (rotation of the chimaeric through 180 degrees) would result in the side of the chimaeric falling to B.Q.'s left still being poorly recognized, whereas if an object-centred code was involved it would be the side that now fell to B.Q.'s right after inversion.

Results of rotating chimaeric faces through 90 and 180 degrees are summarized in Table 2. When the chimaeric faces were inverted (180 degree rotation) B.Q. could not recognize any left sides (20/20 errors) but only made errors to 7/20 right sides (comparison of error rates to left and right sides gives two-tailed binomial $P < 0.05$). Again, left and right refer here to the side of the chimaeric as seen by B.Q. (*see* Fig. 1). This result favours the role of impairment of viewer-centred codes.

We also examined B.Q.'s ability to recognize chimaerics rotated through 90 degrees, so that the chimaeric face lay 'on its side'. B.Q. was asked to keep her head upright as she looked at these chimaerics, and observation of her posture showed that she complied with the instruction. If a viewer-centred code was compromised, her ability to recognize what had been the left sides of upright chimaerics should be improved to the level of

TABLE 2

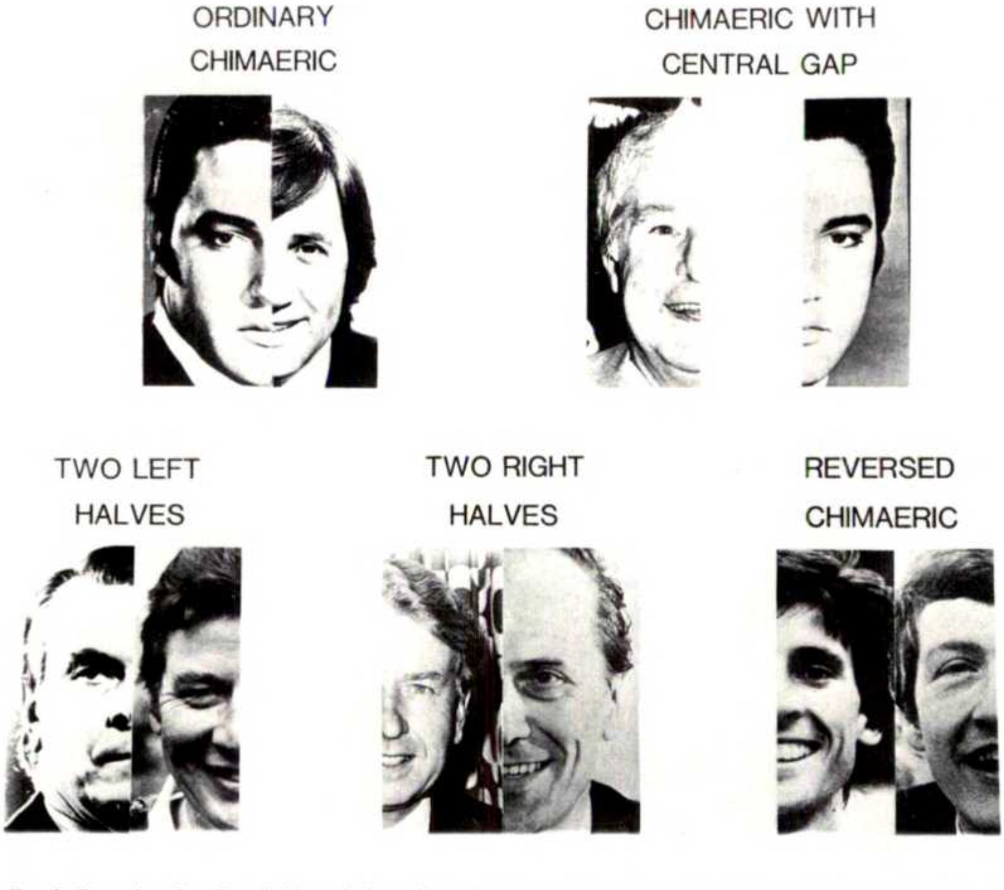
	Left side	*Right side*
Rotated through 180 degrees (inverted)	20/20	7/20
Rotated through 90 degrees ('sideways')	8/20	0/20

B.Q.'s error rates for recognizing left and right sides of chimaeric faces in different orientations (For 180 degree rotations 'left side' and 'right side' refer to the sides of the chimaeric falling to B.Q.'s left or right in this inverted orientation, whereas for 90 degree rotations 'left side' and 'right side' refer to the sides of the chimaeric which would have fallen to B.Q.'s left or right if it was upright.)

right side performance by this transformation, whereas in terms of an object-centred code there should be no improvement. B.Q. made errors to 8/20 of what would have been left sides if the face were upright (three of these errors were with the face positioned horizontally and the hair falling to B.Q.'s left, the other five errors were with the face positioned horizontally and the hair falling to B.Q.'s right) and no errors (0/20) to what would have been right sides if the face were upright (comparison of error rates to left and right side gives two-tailed binomial $P < 0.01$). The result is consistent with the viewer-centred code hypothesis to the extent that her performance to the left sides had improved, but it was still impaired in comparison with the right sides, suggesting that there might be some limited degree of object-centred coding.

Different arrangements of chimaeric faces

In order to determine what it was about a chimaeric face that led to B.Q.'s inability to recognize the left side, different arrangements were examined. These are illustrated in Fig. 2, and the results are summarized in Table 3.



ORDINARY CHIMAERIC

CHIMAERIC WITH CENTRAL GAP

TWO LEFT HALVES

TWO RIGHT HALVES

REVERSED CHIMAERIC

FIG. 2. Examples of 'ordinary' chimaeric face, chimaeric with central 'gap', chimaeric of two left half-faces, chimaeric of two right half-faces, and 'reversed' chimaeric.

TABLE 3

	Left side	*Right side*
Comparison A		
'Ordinary' chimaeric	20/20	0/20
Chimaeric with central 'gap'	4/20	0/20
Comparison B		
Chimaeric of two left half-faces	3/20	1/20
Chimaeric of two right half-faces	5/20	1/20
Comparison C		
'Ordinary' chimaeric	14/20	1/20
'Reversed' chimaeric	1/20	1/20

Comparisons of B.Q.'s error rates for recognizing left and right sides of 'ordinary' chimaeric faces, chimaerics with a central 'gap', chimaerics of two left half-faces, chimaerics of two right half-faces and 'reversed' chimaerics

Three separate comparisons were made. First (Comparison A), B.Q.'s ability to recognize the left and right sides of chimaeric faces was compared for 'ordinary' chimaerics and chimaerics with a central 'gap' corresponding to the width of either half (*see* Fig. 2). Chimaerics with and without the central gap were presented in random order. The presence of the central gap led to a marked improvement in B.Q.'s ability to recognize the left sides of the chimaerics (4/20 errors with a central gap, 20/20 incorrect without a central gap; two-tailed binomial $P < 0.005$).

In a second comparison (Comparison B) chimaerics were made from two left half-faces or two right half-faces (*see* Fig. 2). As Table 3 shows, B.Q. was much better able to recognize the left sides of such chimaerics than ordinary chimaerics, and her performance did not show any significant difference between the recognition of left and right sides of the resulting chimaerics.

For the third comparison (Comparison C) 'ordinary' chimaerics were compared with 'reversed' chimaerics in which the left half-face was placed on the right side of the chimaeric and the right half-face on the left side of the chimaeric (*see* Fig. 2). Ordinary and reversed chimaerics were presented in random order. Recognition of left and right sides was equally good for the reversed chimaerics (1/20 errors to left sides, 1/20 errors to right sides), but recognition of the left side remained severely impaired in the ordinary chimaerics (14/20 errors to left sides, 1/20 to right sides; two-tailed binomial $P < 0.005$).

These investigations show that the key factor in whether or not B.Q. failed to identify the left side of a chimaeric was the extent to which it approximated something the visual system would treat as a single object. When highly salient differences were introduced which would break up the chimaera's resemblance to a single face, the problem was considerably ameliorated.

Position in the visual field

On conventional perimetric testing B.Q. showed a left hemianopia, though Walker *et al.* (1991) found that she could report left visual field stimuli under some conditions. Although she was given unlimited time to compensate for her visual field defect by eye movements in the tasks we have described, we considered it important to establish whether position in the visual field could be responsible for her inability to recognize the left sides of chimaerics. We were particularly concerned to establish whether or not our findings might be accounted for by a tendency to centre fixations on each chimaeric stimulus, thus placing the left side into the area of reduced vision.

Three procedures were used to examine the influence of position of the chimaeric in B.Q.'s field of vision. First, pairs of chimaeric faces were positioned 'side by side', with one chimaeric to the left and one to the right of the other, as in Fig. 3. This task was taken directly from our investigation of K.L. (Young *et al.*, 1990). Data for B.Q. are shown in Table 4. It is clear that her ability to recognize left and right sides of each chimaeric was unaffected by the left or right spatial positioning of the chimaerics themselves (comparisons of error rates to left and right sides: left chimaeric, two-tailed binomial $P < 0.005$; right chimaeric, two-tailed binomial $P = 0.01$). Hence her problem relates to the left side of each object, rather than left or right spatial position.

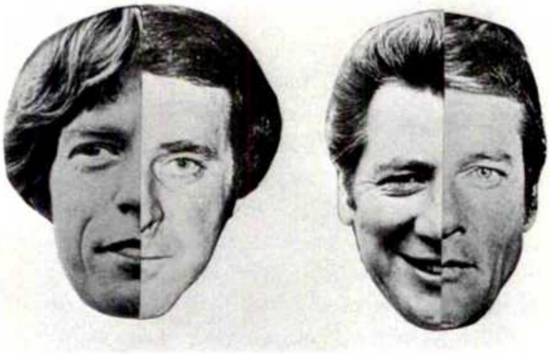


FIG. 3. Example showing arrangement of pairs of chimaeric faces in identification task.

TABLE 4

Left chimaeric		*Right chimaeric*	
Left side	*Right side*	*Left side*	*Right side*
18/20	4/20	18/20	5/20

B.Q.'s error rates for recognition of left and right sides of chimaeric faces positioned left or right of each other.

In this task, the left side of the rightmost chimaeric face must have fallen in B.Q.'s intact right visual field when she was looking at the leftmost chimaeric, yet she still made errors to 18/20 left sides. However, we did not impose any restrictions on the order in which she reported the two chimaerics, so the lack of benefit from right visual field information is not fully convincing. Our second procedure corrected this.

B.Q. was shown a series of chimaeric faces, each of which had a digit directly to its left. She was asked to report the digit first on each trial, and then the parts of the chimaeric. The logic of this procedure is that the chimaeric must have fallen in B.Q.'s right visual field whilst the digit was identified. Faces of six people who had not been used previously in our work with B.Q. were used to create the chimaerics. In 48 trials, she made no errors in reporting the digit, errors to the right side of the chimaeric on only 4/48 trials, but errors to the left side in 47/48 trials (comparison of left versus right side error rates, two-tailed binomial $P < 0.001$). Hence it is clear that the left side of a chimaeric face remained unidentified even if it had fallen in B.Q.'s perimetrically 'intact' field of vision.

The third procedure provided direct confirmation of this finding. Chimaerics made from the faces of five people not used previously in the investigation were presented tachistoscopically in B.Q.'s right visual field. Each chimaeric subtended a horizontal visual angle of 5 degrees, and the midline of the chimaeric was offset by 3 degrees 45 minutes to the right of the fixation point. A presentation time of 200 ms was used to prevent eye movements (*see* Young, 1982), with a pattern mask (consisting of face fragments) following each stimulus. On every trial, a digit was placed between the fixation point and the left side of the chimaeric. B.Q. was asked to report this digit first, and then the parts of the chimaeric. The digit provided a means of fixation control, since central fixation would be needed to report it correctly. Central fixation before each trial was also monitored by watching B.Q.'s eyes, which is a reasonably reliable method (Maddess *et al.*, 1973). Stimuli were presented on back-projected slides, using projectors with Compur shutters controlled by an external timer.

In a block of 15 such tachistoscopic trials, B.Q. made only one error in reporting the digit, and 3/15 errors to the right sides of the chimaerics, but she could not identify the left side in any of the trials (15/15 errors; comparison with right side error rate, binomial $P < 0.01$). Hence she failed to identify the left sides of chimaerics even when they fell in an area of higher acuity (closer to the fovea) than the right sides. As noted in other tests, B.Q.'s inability to identify the left sides of these tachistoscopically presented chimaerics was associated with her insistence that only a single person had been shown on each trial, so that it was not possible to control the order in which she attempted to report left or right sides of the chimaerics.

A block of tachistoscopic trials was also run using digits and left or right half-faces. Apart from the fact that left or right half-faces were presented (instead of chimaerics), the procedure was as for the tachistoscopic chimaeric face trials. The half-faces were positioned in the locations they would have occupied had they been part of a chimaeric. In 10 trials, B.Q. always reported the digit and the half-face correctly (0/5 errors to left half-faces, 0/5 errors to right half-faces). Hence, as we noted in our initial investigations with unlimited presentation time, left half-faces were only particularly hard to recognize when they formed part of a chimaeric.

Chimaeric expressions

Most of the studies we have reported used accuracy of recognition as a convenient index of B.Q.'s ability to process information from the left and right sides of seen objects and faces, but we do not think that her problem relates specifically to recognition. To confirm this, a test with chimaeric expressions was given, based on the procedure devised by Heller and Levy (1981), which had been used in our investigation of K.L. (Young *et al.*, 1990).

Ten people (five men, five women) who were unfamiliar to B.Q. were photographed in smiling and unsmiling full-face poses. These photographs were cut along the vertical midline and joined together to create chimaerics in which each person appeared with one-half of the face smiling, and one-half unsmiling. Each of these chimaerics was accompanied by a mirror-reversed version of the same chimaeric. B.Q. was asked to inspect both faces carefully and choose the one which looked 'happier'. Examples of the task are shown in Fig. 4. It was given with the pairs of chimaeric faces arranged horizontally (Fig. 4B) or vertically (Fig. 4A) in different blocks of trials.

With the horizontally separated chimaerics, B.Q. chose the composite in which the right half-face was smiling as looking happier in 29/40 trials. This significant bias (two-tailed binomial $P < 0.01$) is in the opposite direction to that shown by right-handed normal subjects, who tend to choose the chimaeric with the left side smiling (Heller and Levy, 1981; Levy *et al.*, 1983). For the vertically separated chimaerics, 26/40 of B.Q.'s choices involved the chimaeric in which the right half was smiling. Although in the same direction as that found for horizontal chimaerics, this right-sided preference did not quite reach statistical significance on a two-tailed test (two-tailed binomial $P = 0.08$). For the pooled data from both tasks, there was a highly significant right-sided bias (55/80; two-tailed binomial $P < 0.001$).

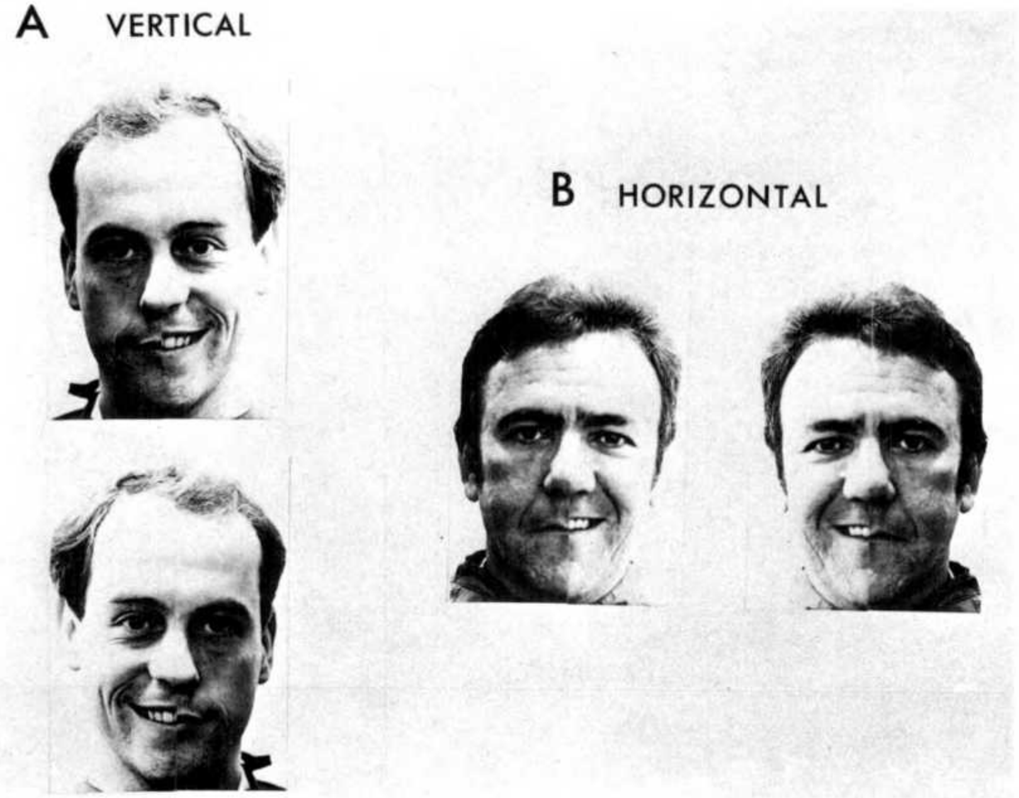


FIG. 4. Examples of stimuli from chimaeric expression tasks.

B.Q.'s bias toward the right side of chimaeric faces in an expression perception task confirms that her problem in making use of the left side was not restricted to recognition tasks.

Insight and awareness

A very striking feature of B.Q.'s performance was her apparent lack of insight into the nature of many of the chimaeric stimuli. Even when shown how the chimaerics were constructed, and told to report both sides, she would often deny that what she was looking at was anything other than a single object or face, and identify only the right side. This was not due to lack of understanding of our instructions, since left *and* right sides were sometimes identified, especially with chimaeric objects or with some of the variants of chimaeric faces we used (*see* Tables 1, 3).

Occasionally, B.Q. became exasperated with our persistence in maintaining that the stimuli were chimaerics, and tried to convince us that there was only a single object. For example, she identified the chimaeric shown in Fig. 5 as 'a bowl', ignoring the rugby ball which made up the left half. When asked what was on the left, she insisted that the whole object was a bowl, and to demonstrate this she spontaneously traced around the rim with her finger, along the trajectory shown in Fig. 5. To do this, she must have needed some visual guidance for the finger movement, yet she made no comment even when her finger passed across the left side of the chimaeric, where there was no trace of the rim.

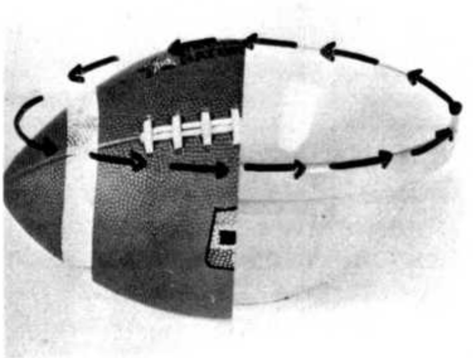


FIG. 5. B.Q.'s demonstration that only a single object was present, by tracing the bowl's rim.

Intrigued by this observation we asked B.Q. to trace around the contours of other chimaeric objects. To make the contours more salient, these chimaerics were made from line drawings. Occasionally, B.Q. would trace non-existent contours on the object's left (as in Fig. 5), but more often her tracing was reasonably accurate. Figure 6 shows an example. Yet when asked to identify the parts of the chimaeric objects whose contours she had traced correctly, B.Q. still relied on the right side of each. Thus with Fig. 6, she traced the contours of the saucepan (right half) and the pig (left half) accurately, then identified it as 'a pan'. When asked directly about the part on the left she could only suggest that 'It must be vegetables in the pan; parsnips or maybe potatoes'.

A similar phenomenon was found with chimaeric faces. If we pointed to parts of the

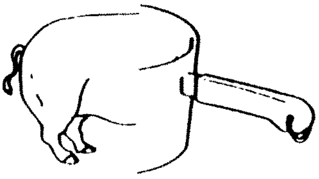


FIG. 6. Chimaeric line drawing of pig (left half) and saucepan (right half). B.Q. traced its contour accurately, but identified it as a pan. When pressed she suggested that the left part 'must be vegetables in the pan; parsnips or maybe potatoes'.

chimaeric on the left, B.Q. could describe them accurately, yet she nearly always identified the chimaeric as the right half-face. For example, with a chimaeric in which the left half came from Mick Jagger's face and the right half from Roger Moore, she described accurately the shape of the left eye, the long hair over the left ear, the full lips on the left, and the stubble on the left chin when we pointed to these features. We chose these features because none of them resembled the parts of Roger Moore's face on the other side of the chimaeric, yet even after describing all of these features of Mick Jagger's face successfully B.Q. identified the chimaeric only as Roger Moore, and did not accept that part of another person's face was present. On another occasion she showed partial insight; when made to describe parts of a face chimaeric with the left half of Michael Parkinson and the right half of Terry Wogan, she commented, 'It's Terry Wogan . . . but there's a touch of a Picasso about him.' Full insight into the fact that the stimuli were chimaeric was rare, but sometimes noted; for example, with a face chimaeric of the left half of Elvis Presley and the right half of Steve Davis, B.Q. commented that it was 'Elvis Presley . . . but there's a bit of Steve Davis somewhere', and then noticed there were 'two faces stuck together'.

These observations show that even when B.Q. must have seen the features on the chimaeric's left (because they were accurately traced or described), they would often fail to influence her identification of the chimaeric, which remained entirely dominated by the right half. In other cases, this right-half dominance was so great that left-half features were effectively confabulated (as in Fig. 5). Here it is difficult to determine whether B.Q. really thought she 'saw' these features, or if she was assuming that they 'must' be there, but her insistence seemed to us to indicate that she was 'seeing' them.

To examine the severity of her lack of insight into the chimaeric stimuli, we showed B.Q. a randomly ordered series of 20 chimaeric faces and 20 normal face photographs. On each of the 40 trials, B.Q. was asked whether the stimulus was a normal face or a chimaeric face. She made errors on 17/40 trials, showing an overall level of performance which was not significantly different from chance, with a pronounced tendency to claim that the stimuli were not chimaerics (0/20 errors to normal faces, 17/20 errors to chimaeric faces) even though there was (to us) an obvious 'join' along the midline of each chimaeric. To eliminate this bias toward denying that stimuli were chimaerics, the task was repeated with a forced-choice procedure in which a chimaeric face and a normal face were simultaneously presented. On each of the 40 trials, B.Q. was asked to choose the chimaeric. She was correct on 33/40 trials, which is above chance (two-tailed binomial $P < 0.001$) but obviously far from normal in what is a trivially easy task for normal people. Even when her choices were themselves correct, her reasons were often extraordinary, relating to irrelevant details such as a tear in the photographic paper on the right-hand edge of one of the chimaerics (*cf* Bisiach and Rusconi, 1990).

Defining features

The thrust of much of the work reported here is to demonstrate that B.Q. often did not make effective use of information from the left side of visual stimuli. However, this was not inevitably so. We first came to appreciate this when we tried to replicate the observations made by Marshall and Halligan (1988), who had shown that a neglect patient who could not state the difference between a normal picture of a house and one in which there were flames emerging from the left-hand side nonetheless consistently chose the non-burning house as the one she would prefer to live in. When given this task, to our considerable surprise B.Q. immediately remarked that 'this one's got fire coming out of the window'. The task was then abandoned, but the observation proved instructive.

Kartsounis and Warrington (1989) and Seron *et al.* (1989) have reported that features on the left of an object or scene can influence the interpretations made by neglect patients if they contribute essential information. From the 'burning house' incident, it seemed likely that the same might hold for B.Q.

We investigated this possibility both with objects and faces. For objects, we took several line drawings from the Snodgrass and Vanderwart (1980) series for which the view was asymmetric and there seemed to us to be an essential defining feature on the left- or right-hand side. Examples are shown in Fig. 7. These object drawings were then cut into left and right halves, and one half-drawing of each object was shown to 12 normal people (six people were shown the left halves, and six were shown right halves) who were asked to recognize them. In this way, we were able to assemble a set of 16 object drawings in which eight of the objects were always recognized from the half containing the defining feature (0/6 errors) and never recognized from the other half (6/6 incorrect), and the other eight objects were again always recognized from the half containing the defining feature (0/6 errors) and seldom recognized from the other half (always more than 3/6 incorrect).

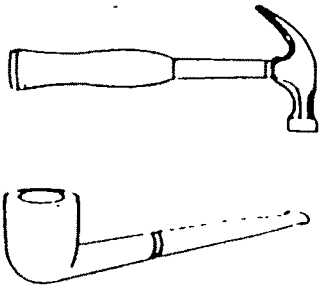


FIG. 7 Object drawings with defining feature on left (pipe) or right (hammer).

These 16 drawings were printed in original and mirror-reversed orientations, so that the defining feature could be on the left or right (*see* Fig. 7). They were shown to B.Q. in both orientations, arranged into a pseudo-random order in which one example of each object was shown in a first block of trials (half of these with defining features on the left, half with defining features on the right) and the other (reversed) example of each drawing occurred in the second block of trials. She made errors in recognizing

4/16 of the drawings with defining features on the left, and 2/16 with defining features on the right. The importance of this result lies in the fact that it demonstrates that B.Q. could make some use of left-side information when it was critical in determining the object's identity (since 12/16 of the drawings with defining features on the left were recognized correctly), which is in contrast to her poor use of left-sided information from chimaerics.

A comparable finding was made for faces, using a different procedure. Twenty photographs of famous people were digitized, and the internal features from the right side of each face were removed with a paint program. Figure 8 shows an example. Internal features are particularly important in the recognition of familiar faces (Ellis *et al.*, 1979; Young *et al.*, 1985), so we considered that this manipulation would make identification of the faces dependent on left side information. To check how useful the degraded right sides would be in recognizing the faces, these were also separated from the left sides and presented in isolation (*see* Fig. 8).

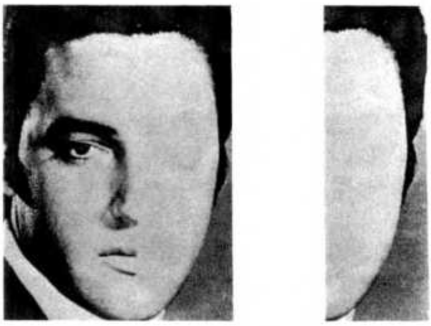


FIG. 8. Face and right half-face with internal features masked.

When these stimuli were shown to B.Q. she made errors to 8/20 of the faces with the right-sided internal features obscured, but to 19/20 of the right sides of the same stimuli presented in isolation (comparison of correct recognition rates, two-tailed binomial $P < 0.005$). Hence her recognition of several of the faces without internal features on the right must have been based on the use of information from the left sides of the stimuli. Again, the contrast with her inability to use left-sided information from chimaerics is striking.

Reading

We noted that when reading B.Q. often omitted words from the left side of the page, but was usually accurate for the words she did attempt. Thus she made one of the types of error usually found in cases of 'neglect dyslexia' (omissions from the left side of the page), but did not show the misreadings of initial letters of words which have also been noted (Kinsbourne and Warrington, 1962; Ellis *et al.*, 1987; Young *et al.*, 1991). Table 5 summarizes B.Q.'s error rates in reading words, non-words and numbers.

B.Q. was asked to read a list of words whose first letter could be substituted to make another word or deleted to leave a complete word (for example, CLOVE, which can form GLOVE after substitution of the initial letter, or LOVE by deletion). These words

TABLE 5

	Example	*Errors*
Words with first letters which can be substituted or deleted	CLOVE	1/57
Compound words		
Non-contiguous	EGG CUP	0/20
Contiguous	EGGCUP	0/20
Scrambled compound words		
Non-contiguous	TIP CAP	0/20
Contiguous	TIPCAP	1/20
Pronounceable non-words	SHEEM	5/30
Letter strings		
Four-letter	UNJQ	0/10
Five-letter	TLWVU	3/10
Six-letter	WCTFQZ	6/10
Numbers		
Four-figure	5902	1/10
Five-figure	73297	3/10
Six-figure	829412	4/10

B.Q 's error rates in reading words, pronounceable non-words, letter strings and numbers

were chosen to allow us to determine the extent to which B.Q. was prone to initial-letter misreadings. Only 1/57 of these words was misread. Although the only error she made involved the initial letters (CLOVE misread as 'glove'), 56/57 of the words were read correctly. This is a very much lower rate of initial-letter misreadings than has been noted in some other neglect patients (Ellis *et al.*, 1987; Young *et al.*, 1991).

Behrmann *et al.* (1990) found that a neglect patient, H.R., made errors involving failing to report the leftmost of two simultaneously presented words (e.g. SUN TAX), but that this tendency was reduced for compound words (e.g. COW BOY) in which the two words form a meaningful whole, and further reduced if these compound or non-compound words were made physically contiguous (COWBOY, SUNTAX).

This procedure was tested with B.Q. She was shown 20 pairs of compound words (EGG CUP), and 20 pairs of non-compound words (scrambled compounds, such as TIP CAP). These were printed in Futura Medium 24 point upper-case lettering, and presented with or without a space between the words (EGG CUP versus EGGCUP). The compound word pairs were read perfectly by B.Q. in both conditions (0/20 errors to non-contiguous pairs, 0/20 errors to contiguous pairs), and B.Q. only made one error to non-compound pairs (0/20 errors to non-contiguous pairs, 1/20 errors to contiguous pairs; the error was to report TEASTY as 'tasty').

Her relatively well preserved reading of words can be seen as consistent with our findings indicating that B.Q. could make use of information from the left side of objects and faces when this was critical to determining identity. For word recognition, the initial letters (i.e. the word's left side) are very often crucial in deciding exactly which word it is. Representations involved in word recognition will therefore make considerable use of left-sided information.

The importance of pre-existing representations can be seen in B.Q.'s reading of non-words, which was poor in comparison with words. She made errors in reading 5/30 pronounceable non-words, with all five errors involving initial letters. Decreasing the order of approximation to English (by using letter strings) led to 9/30 letter strings being incorrectly reported. Again, all B.Q.'s errors involved initial letters (mostly omissions rather than substitutions), and there was also a marked effect of length (0/10 errors to four-letter strings, 3/10 errors to five-letter strings, 6/10 errors to six-letter strings). The initial digits of large numbers were also misread (8/30 incorrect; 1/10 errors to four-figure numbers; 3/10 errors to five-figure numbers; 4/10 errors to six-figure numbers; errors were mostly omissions rather than substitutions of initial figures). Poorer reading of non-words than words has also been reported in some other neglect cases (Sieroff *et al.*, 1988; Behrmann *et al.*, 1990).

DISCUSSION

B.Q. showed a striking inability to identify the left sides of chimaeric objects and faces. Often, she would deny that the stimulus was chimaeric at all, and she was remarkably poor (though above chance) at discriminating chimaeric from normal faces even in forced-choice. Sometimes (as in Fig. 5) left-sided details were inferred or extrapolated from the right side, making it difficult for us to determine whether she really thought she 'saw' them, though she certainly acted as if this was the case. Even when left-sided details had obviously been 'seen properly', because B.Q. had traced or described them accurately, they were either ignored in reporting the identities of the constituent parts of the chimaeric or assimilated in some way to the information from the right side (as in her description of the 'pig' part of Fig. 6 as 'vegetables in the pan; parsnips or maybe potatoes').

Neglect of the left side was more pronounced for chimaerics which approximated an individual face or object. When left half-faces or half-objects were presented in isolation, B.Q.'s ability to recognize them was much better than when they formed part of a chimaeric. If the parts of a chimaeric face obviously violated the overall face shape, by having a gap in the middle, by using two left or two right halves, or by reversing the spatial positions of left and right halves. B.Q. did not neglect the left half to such an extent (*see* Fig. 2 and Table 3).

The problem with the left side occurred regardless of the chimaeric's position in B.Q.'s field of vision, and was even found with brief (200 ms) presentations of stimuli confined to her (perimetrically intact) right visual field. Hence it cannot be attributed to her left visual field defect on conventional perimetric testing, or to defective control of eye movements. When chimaeric faces were inverted, B.Q. continued to neglect the side of the chimaeric falling to her left, which implies that the neglect did not operate in entirely object-centred coordinates.

We have noted that the left side of objects was not always completely ignored. With chimaeric stimuli, accurate tracings or descriptions of left-half features could often be made. Even when this was done, though, features from the right side were given excessive weight and there was usually no more than partial insight into the discrepancies between left and right sides. However, left-sided information could be used if it was critical in determining the identity of an object or a face (Figs 7, 8). We suggest that this could account for B.Q.'s lack of neglect of individual words, for which left-sided (initial) letters are often crucial to successful recognition.

We will discuss further two aspects of this case. First, how best to account for B.Q.'s deficit, and secondly the relation between her case and other cases and observations in the literature on visual neglect.

Accounting for B.Q.'s deficit

Behrmann *et al.* (1990) have proposed an interesting account of neglect dyslexia which we think could also be useful in explaining B.Q.'s deficit. They described two neglect dyslexia cases, A.H. and H.R., with contrasting patterns of impairment. A.H. was more affected than H.R. by manipulations affecting relatively 'low-level' representations (such as changes in word length), whereas H.R. was more affected than A.H. by 'higher-order' factors such as lexical status (word or non-word). However, because both patients did show both types of effect (albeit to different degrees), Behrmann *et al.* (1990) proposed that the differing patterns of deficit can be accounted for in terms of the interaction between higher-order knowledge of words and a single locus of attentional impairment affecting an early processing stage.

Behrmann *et al.* (1990) assumed that this early processing impairment did not have an all-or-none influence, but was unevenly distributed as a gradient from left to right. Even though features on the left were poorly picked up, they may have continued to activate top-down knowledge if the gradient was not too severe, which could have accounted for the presence of 'higher-order' (lexicality) effects for H.R. For A.H. with the more severe left-right gradient of impairment (as shown by his greater susceptibility to 'low-level' manipulation), the analysis of features on the left was too impaired for interaction with higher-order representations to be effective.

This account is directly applicable to B.Q.'s reading. She showed a pronounced lexicality effect, with few errors in reading words but greater difficulty with non-words. For letter strings and numbers, length affected her ability to report them correctly, whereas words of the same length could be read without error. These findings confirm the presence of a left-right gradient (errors to initial letters of pronounceable non-words and letter strings, and initial digits of numbers) affecting an early stage of processing (length effect on reporting letter strings and numbers), with preserved interaction with higher-order knowledge (better reading of words than non-words).

Behrmann *et al.*'s (1990) work was only concerned with neglect dyslexia, but we see no reason why the principles underlying their account should not be extended to B.Q.'s other visual recognition problems. Deficient encoding of the left side of visual stimuli was evident in her performance in our chimaeric expressions task, where the face stimuli were those of unfamiliar people, so that interaction with pre-existing representations of these faces could not arise. It is of interest, however, that her right-sided bias in this task was not pronounced, suggesting a relatively shallow left-right gradient which would meet Behrmann *et al.*'s (1990) criterion for the possibility of preserved interaction with higher-order knowledge. Such interactions were evident when B.Q. was shown objects or faces which could only be recognized using left-side features (Figs 7, 8). Indeed, the basic finding that she could recognize left half-faces presented in isolation can be seen as reflecting the same phenomenon.

Where B.Q. showed pronounced difficulties with left-side information was in the tasks using chimaerics made from familiar visual stimuli (everyday objects or famous faces). However, these could also reflect interactions with higher-order knowledge if we consider that the visual recognition system will usually recognize one object (or face) at a time. A technique used in some computer simulations of visual recognition (e.g. Burton *et al.*, 1990) involves increasing the excitation of representations of the face or object seen, whilst simultaneously using inhibitory connections to suppress the identities of other objects or faces. This helps the system to achieve unambiguous recognition. If the human visual recognition system works in a similar way, then any degraded pick-up of left-side information from a chimaeric stimulus could result in the identity of the left side being suppressed by the constantly competing right side. This interaction with higher-order knowledge could also account for the cases in which B.Q. effectively confabulated or extrapolated left-side features (as in Fig. 5).

A relatively 'early' locus of impairment is also implied by our finding that B.Q.'s neglect did not operate in what in Marr's (1982) terms would be object-centred coordinates (since she continued to neglect the side of inverted-face chimaerics falling to her left; inversion would reverse the direction of neglect with a truly object-centred code). However, it is important that the neglected coordinates were not retinal; left-sided neglect was found even to stimuli that had fallen only in the right visual field. This implies a degree of object-based coding, in that the problem affected the left side of an individual object regardless of where it had fallen in B.Q.'s field of vision. However, this object-based coding could largely involve what Marr (1982) would have considered a viewer-centred code of the object itself. The key point is that the left-right gradient of deficit applied most strongly to the features of something B.Q.'s visual system had coded as an individual object, as the results for different arrangements of chimaerics demonstrate (Fig. 2 and Table 3).

Relation to other cases and observations in the literature

There are some instructive comparisons to other cases and observations in the literature. Although there have been relatively few studies of neglect of objects, we have noted that Kartsounis and Warrington (1989) and Seron *et al.* (1989) also observed that if the left side of an object or scene was crucial to determining its identity or meaning then it could be used by neglect patients. We might now want to add the caveat that this would only be expected if the left-right gradient of impairment was not very steep. This could account for Marshall and Halligan's (1988) observations of a patient who obviously encoded the burning left side of a house (since she did not choose it as one she would prefer to live in) whilst giving no conscious acknowledgement of this. In such a case, the left-right gradient would be steeper than for B.Q., who immediately acknowledged that the house was on fire.

Bisiach and Rusconi (1990) tried to replicate Marshall and Halligan's (1988) observations in a series of four neglect patients, with only partial success. Again, the limited success might well reflect differences in slope of the left-right gradient of deficit for each patient. Interestingly, though, Bisiach and Rusconi (1990) did make observations similar to some of those reported here. They found that when asked to detect left-sided differences between two drawings, their patients performed poorly and seemed to confabulate many responses. Even when asked to trace around the drawings with their fingers, full insight into the left-sided discrepancies was achieved in only one of 10 trials. Hence, like B.Q., Bisiach and Rusconi's (1990) patients were quite capable of passing their finger across the anomalous area of a picture (presumably with visual guidance) without detecting anything unusual. This happened in seven out of 10 of Bisiach and Rusconi's (1990) tracing trials. In the remaining two trials, patient R.C. showed partial insight very like that we occasionally found with B.Q. (Fig. 6); for example, after tracing the Marshall and Halligan (1988) houses with his finger he pointed to the flames and said 'Maybe there is something here. But what is it?'

Some of these observations are reminiscent of the phenomenon of 'completion' of visual forms across hemianopic field defects. An investigation of this was made by Warrington (1962), who reported that patients with parietal lobe lesions reported seeing complete shapes when half of a visual form was presented such that its 'missing' part would have fallen in the hemianopic area. The difference, though, is that B.Q. and the patients described by Bisiach and Rusconi (1990) experienced completion even when missing or contradictory information fell in an otherwise intact area of the visual field. At the very least, this implies that the phenomenon operates at a 'higher' level than retinotopic coordinates.

We now return to the comparison of B.Q. and the case we previously investigated, K.L. recognized the left and right sides of objects with equal ease, whereas he was impaired at recognizing the left half of faces both in chimaerics *and* when they were presented in isolation.

Like B.Q. then, K.L. showed neglect of the left side of chimaeric faces, but unlike B.Q., K.L.'s problems were also severe to the left sides of faces presented in isolation. We do not claim that B.Q. was entirely free from problems with left sides in isolation, but they were nothing like as marked as for K.L. Also, although K.L. had problems in recognizing the left sides of faces presented in isolation, equivalent difficulties were not found for other visual stimuli, including objects and car fronts. His problem, unlike B.Q.'s was face-specific.

Some of these differences can be accounted for by proposing that the left-right gradient of a deficit affecting face-based coordinates was more steep for K.L. than B.Q., resulting in problems even to left half-faces in isolation. In favour of this suggestion is the fact that K.L. showed a more pronounced asymmetry to chimaeric expressions (Fig. 4) than B.Q. We have pointed out that because these involved unfamiliar faces, the possibility of interaction with pre-existing representations does not arise, and that B.Q. showed a relatively shallow left-right gradient on this task (55/80 right-sided choices overall). K.L. though, was much more right-biased here (73/80 right-sided choices; comparison with B.Q., Fisher exact $P < 0.001$), which is consistent with the claim of a more steep left-right gradient for K.L.

There still remains the domain-specific nature of K.L.'s deficit, which affected only faces, whereas B.Q. had equivalent impairments of face, object and perhaps word recognition. One possibility is that B.Q.'s impairment arose earlier in the visual system, at a stage where domain-specific representations are not involved. If this is correct, further case studies will be able to demonstrate other domain-specific forms of neglect when the impairments are centred on relatively late stages.

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FOCAL RETROGRADE AMNESIA FOLLOWING BILATERAL TEMPORAL LOBE PATHOLOGY

A NEUROPSYCHOLOGICAL AND MAGNETIC RESONANCE STUDY

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SUMMARY

A patient who suffered a severe closed head injury was left with a dense retrograde amnesia for events which she had experienced prior to her injury, but she showed only mild, patchy anterograde memory impairment. Her retrograde amnesia included both public events and autobiographical material, and it extended back to her childhood. Previously learned skills such as playing a piano and driving a car were spared, even though she had no recollection at all of the original learning experience. A series of focused magnetic resonance scan images revealed major pathology in the anterior portion of both temporal lobes. No significant abnormality was found in the hippocampus, thalamus or other medial structures in the limbic-diencephalic system. Our findings indicate the independence of anterograde and retrograde memory mechanisms, and point to structures and pathways in the anterior temporal lobes as playing a critical role in memory for past events.

INTRODUCTION

In many memory disordered patients, major anterograde memory loss is accompanied by marked retrograde memory deficits (Kapur, 1988). However, a number of patients may present with minimal retrograde memory deficits or retrograde deficits which are disproportionately small compared with their anterograde memory impairment (e.g. Zola-Morgan *et al.*, 1986). Patients in whom retrograde amnesia occurs as a relatively isolated deficit, or disproportionately marked compared with any anterograde memory loss, form a relatively unique set of patients. A few such neurological patients have been reported in recent years (Roman-Campos *et al.*, 1980; Goldberg *et al.*, 1981; Rousseaux *et al.*, 1984; Kapur *et al.*, 1989).

We were able to examine a head injury patient who was similar in a number of ways to the cases described by Goldberg *et al.* (1981) and by Rousseaux *et al.* (1984). We therefore sought to carry out the following investigations: (1) to administer a wide range of anterograde and retrograde memory tests to see if a similar selectivity of retrograde memory loss was present; (2) to ascertain the extent, severity and sparing of retrograde memory functioning; (3) to obtain precise neuroradiological information, based on magnetic resonance imaging, relating to the possible anatomical basis of focal retrograde amnesia. Anatomical speculations from single case studies of global amnesic patients,

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such as those who have suffered herpes simplex encephalitis (Damasio *et al.*, 1985), are limited by the coexistence of diverse loci of lesions. On the basis of CT scan data from their head injury patient, Goldberg *et al.* (1981) suggested that a lesion in the ventral tegmental region of the mesencephalon may underlie focal retrograde amnesia. However, there has been no subsequent evidence to confirm or refute this hypothesis, or to suggest other candidate anatomical structures which may underlie dense retrograde amnesia. Furthermore, since the publication by Goldberg *et al.* (1981), magnetic resonance imaging technology has become widely available, offering greater anatomical precision than computerized axial tomography.

CASE REPORT

Clinical history

L.T., a right-handed woman (date of birth November 2, 1962) who had previously worked as a nanny, suffered a severe closed head injury in November 1988 as a result of falling off a horse. A skull X-ray indicated a left occipital fracture. A CT scan at the time of hospital admission was reported as follows: 'Both cerebral hemispheres are smeared with fresh subarachnoid blood. Haemorrhagic contusion of the right frontal lobe is present, possibly also of the left frontal lobe. The quadrigeminal cistern is poorly outlined and appears to be compressed, but the third ventricle remains visible.' After several days ventilation, L.T. was weaned off this support and was gradually improving until she became pyrexial on December 5 with a deterioration in her level of consciousness. A repeat CT scan showed no evidence of an intracranial abscess, and on this occasion the scan was reported as showing patchy low attenuation in the white matter of both frontal lobes, more so in the right than the left, with possible involvement of the right temporal pole. The ventricles had now returned to a more normal appearance.

Her past medical history contained no events of note. She left school at the age of 16 yrs. with six O-level passes, and then completed a 2-yr course to become a qualified nanny. Detailed neurological and neuropsychological investigations were carried out between April and June 1990

Physical examination

She was alert, attentive, cooperative and appropriate in her behaviour during the examination. She walked on a slightly widened base with a mildly irregular cadence but was able to walk heel to toe and could hop on either leg. No sense of smell could be detected. Her visual acuity was 6/6 bilaterally (corrected) and the optic fundi were normal. There was a mild divergent strabismus which was constant in all directions of gaze and associated with diplopia. Some convergence occurred but this could be maintained for close objects only with difficulty. With an ophthalmoscope, a slight vertical nystagmus could be detected especially in the right eye where the vertical phase was downwards. The pupils were of normal size, equal in circumference and reacted briskly to light and accommodation. There was a very slight right ptosis. Her corneal reflexes were both present. There was a slight weakness of the left side of the face which included the orbicularis oculi as well as the muscles of the lower part of the face. There was mild impairment of hearing in the left ear associated with an old perforation of the drum. Sensation on the face, mouth and palate were normal and voluntary movements of the palate also appeared normal, but no gag reflex could be obtained and stimulation of the back of the pharynx did not induce a sense of discomfort.

The upper limbs were held outstretched to command a normal posture. Fine movements of the right hand were normal, but rapid and discriminatory movements of the digits of the left hand were moderately impaired. Tendon reflexes were pathologically brisk in both upper limbs but there was no increase in muscle tone. There was mild weakness of all muscle groups in the left upper limb reducing power by approximately 15% compared with the right side.

In the lower limbs there was an equivalent reduction in power in all muscle groups. Muscle tone was normal. Plantar responses and abdominal reflexes were all normal. Tendon reflexes were pathologically brisk, with unsustained clonus at the knees and at the right ankle and sustained clonus at the left ankle. Rapid voluntarily alternating movements of the foot were impaired on the left side. There was no abnormality of sensation either in the upper or lower limbs.

These findings provided limited clinical evidence for a brain stem lesion impairing conjugate gaze and possibly contributing to impaired motor control in the limbs, although some of the impairment on the left side is likely to have been due to impairment of motor pathways in the right hemisphere. The duration of her post-traumatic amnesia was assessed in May 1989 to be around 3 mths.

Brain imaging

Magnetic resonance imaging (MRI) was carried out in April 1990 using a Philips 0.5 Tesla Gyroscan T5 scanner. A protocol similar to that used by Press *et al.* (1989) was followed so as to obtain dedicated views of candidate anatomical regions important for memory, such as structures in the limbic-diencephalic system and the temporal lobes. The hippocampus was examined in particular detail.

Magnetic resonance scanning comprised an initial sagittal T_1W survey, followed by coronal T_1W inversion recovery (TE = 30; TR/IR = 1500; T1 = 400), transverse and coronal T_2W sequences (TR SE = 2186; TE = 30) and a sagittal midline T_1W sequence. We have attempted to assign Brodmann numbers to the areas of abnormal signal, though we accept that there is inevitably some margin of error in the allocation of such numbers. High T_2W responses were obtained from both temporal lobes, and these were evident on axial views of mid (Fig. 1A) and low (Fig. 1B) cuts of the temporal lobes. In the mid view of the right temporal lobe (Fig. 1A), damage was evident in the area of the temporal pole (Brodmann's Area 38), anterior middle temporal gyrus (Brodmann's Area 21) and anterior parahippocampal gyrus (Brodmann's Area 28), and in the mid view of the left temporal lobe (Fig. 1A) a similar but less extensive lesion was present, sparing the parahippocampal gyrus (Brodmann's Area 28). In the low view of the right temporal lobe (Fig. 1B), damage was evident in the anterior middle temporal gyrus (Brodmann's Area 21), and the temporal pole (Brodmann's Area 38). Magnified views of the hippocampus in the patient L.T. (Fig. 1C) failed to yield evidence of any abnormality, as compared with that of the matched normal control subject (Fig. 1D). On the basis of a high-powered mid-coronal cut, we were able to identify the major structures within the left hippocampal formation, and these were equally prominent in L.T. as in the control subject. The only other abnormalities of note in L.T.'s HR scan were mild ventricular dilatation and high T_2W signals from the infero-medial portion of both frontal poles.

General cognitive functioning

Before her detailed assessment at the Wessex Neurological Centre between April and June 1990, L.T. had been seen by a clinical psychologist for a brief assessment 2–3 mths after her head injury. He reported that she had mild anterograde memory impairment and mild visuoperceptual impairment, together with considerable behavioural changes which included euphoria, distractibility and some disinhibition. On the basis of nine subtests of the Wechsler Adult Intelligence Scale (Revised) (Wechsler, 1981) given in March 1990, L.T. had a verbal IQ of 92, a performance IQ of 108 and a full-scale IQ of 98. Individual subtest scores are shown in Table 1.

On the National Adult Reading Test (Nelson, 1982), her reading score was equivalent to an estimated IQ of 105. As can be seen, most subtest scores were within the normal range, but her scores on the Information subtest, and to a lesser extent the Vocabulary subtest, do probably represent a significant impairment. The Information subtest includes items which cover remote memory and general knowledge, and this contributed to her low score on this task. On the modified Wisconsin Card Sorting Test (Nelson, 1976), she obtained a perfect score. On the verbal fluency subtest of the Minnesota Multiphasic Aphasia Examination (Benton and Hamsher, 1978), she did not show any impairment. Her naming of a set of line drawings (McKenna and Warrington, 1983) was mildly impaired (13/30 items correctly named), though there was no evidence at all of any dysphasia in her conversational speech. She performed well on a faces matching task (Benton *et al.*, 1975).

Anterograde memory assessment

L.T. did not complain of any significant everyday memory difficulties, and her fiancé also thought her everyday memory was normal, these observations being borne out by formal scores on a memory symptoms test sensitive to memory difficulties after blunt head injury (Kapur and Pearson, 1983). L.T.'s anterograde memory functioning was assessed over a range of tests. Her performance on the Revised Wechsler Memory Scale (Wechsler, 1987) is outlined in Table 2.

As can be seen, her general and delayed memory quotients were both within normal limits (92 and 104, respectively). On closer scrutiny of individual subtests, the only memory subtest on which she had any difficulty of note was the story recall task; this was probably due in part to her mild naming difficulty.

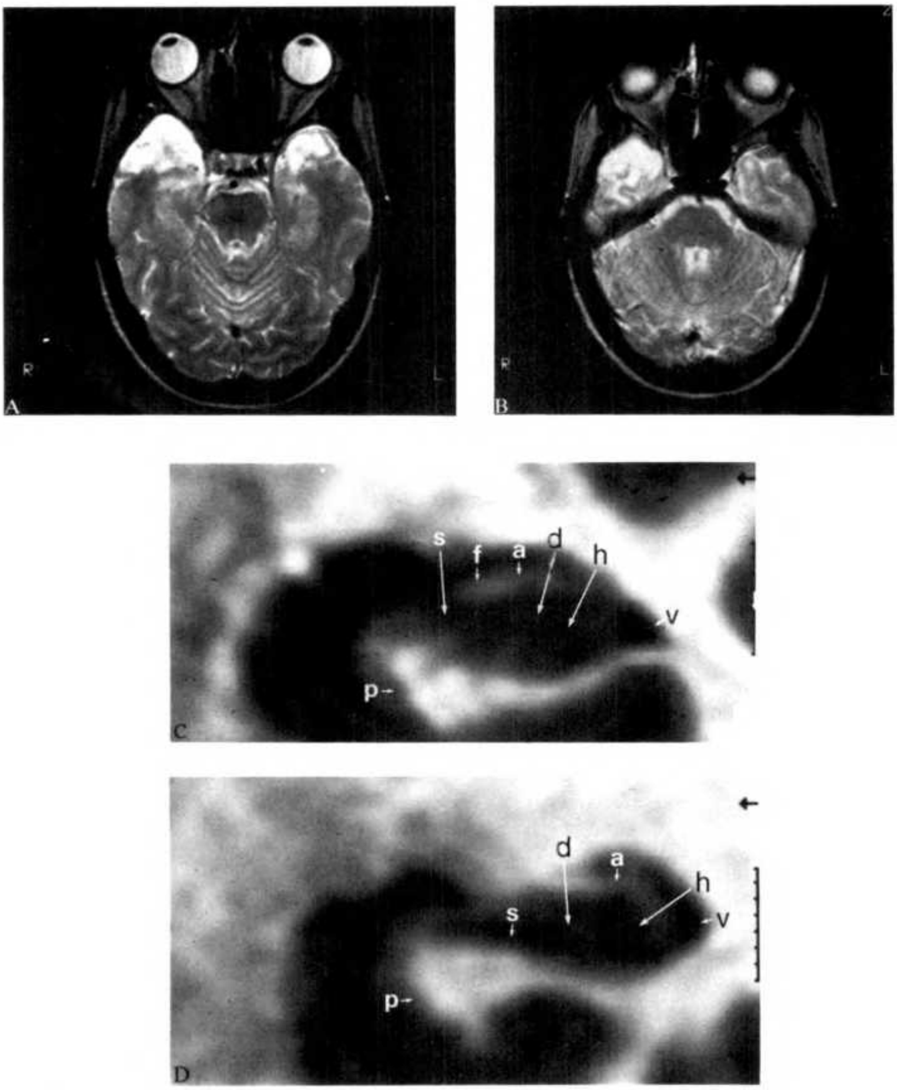

FIG. 1. Magnetic resonance scans of patient L.T. and of an age-matched normal control subject. Axial views of mid (A) and low (B) cuts of the temporal lobes. Magnified views of the hippocampus in the patient L.T. (C) and in control subject (D) (a = alveus; f = fimbria; d = dentate gyrus; h = hippocampus; p = parahippocampal gyrus; s = subiculum; v = ventricle of temporal horn).

It is worth noting that on delayed recall she was in fact able to remember most items which she retrieved on immediate recall. On a word and a face recognition memory test (Warrington, 1984), she obtained a perfect score (50/50) for word recognition, but did show a moderate impairment (37/50: age-scaled score of 5) on the faces recognition memory task.

Retrograde memory assessment: autobiographical memory

L.T.'s autobiographical memory for events prior to the head injury was assessed by means of a structured interview covering past personal events, and used similar procedures to those described elsewhere

TABLE 1 L.T.'s PERFORMANCE ON THE WECHSLER ADULT INTELLIGENCE SCALE—REVISED

	Verbal IQ	*Performance IQ*	*Full-scale IQ*	*Subtest scores (age-scaled)*
WAIS-R	92	108	98	Information, 4 Arithmetic, 10 Similarities, 9 Digit span, 13 Vocabulary, 7 Digit symbol, 12 Block design, 10 Picture arrangement, 11 Picture completion, 12

TABLE 2 L.T.'s MEMORY TEST SCORES

Test	*Raw score*	*Statistic score*
Verbal memory and learning		
Word recognition	50/50	13 (scaled score)
Story recall (immediate)	16/50	13 percentile
Story recall (delayed)	18/50	31 percentile
Verbal paired-associate learning	20/24	
Word-list learning		
List one	50/75	50 percentile
List two	8/15	75 percentile
Delayed recall		
List one	14/15	79–90 percentile
Visual non-verbal memory and learning		
Faces recognition	37/50	5 (scaled score)
Designs recall (immediate)	39/41	96 percentile
Designs recall (delayed)	38/41	93 percentile
Pattern-colour		
Paired-associate learning	18/18	
Design learning		
Design one	45/45	>90 percentile
Design two	7/9	75–80 percentile
Delayed recall		
Design one	9/9	75 percentile
General memory quotient		92
Delayed memory quotient		104

(Borrini *et al.*, 1989; Kopelman *et al.*, 1989). The particular items selected for this interview were based on an initial interview with L.T.'s fiancé, and covered the following areas: holidays, hospital treatments, occupational history, houses in which she had lived, cars which she had owned, educational experience, births and deaths in her family, and weddings she had attended. The interview schedule was given twice, once to cover the time period prior to her injury, and on a second occasion 5 wks later to cover post-injury events in the past year. Autobiographical memory is notoriously difficult to assess precisely and in a reliable and quantitative form in view of individual differences which undoubtedly occur between subjects. We have tried to take this into account in our interpretation of L.T.'s responses.

L.T. had marked loss of memory for information and events relating to the period prior to her injury, and (unusual for patients with neurological disease) both L.T. and her family were also acutely aware of this disability and spontaneously offered this as the major residual disability which she now displayed. For example, although she had known her fiancé for almost 9 yrs she had no memories of their time together and could not recount when she first met him. Her 'personal semantic' memory (covering tasks such as the ability to name schools attended, addresses where she had lived, etc.) was markedly impaired, though generally less severely affected than her 'personal episodic' memory for specific incidents and events which had taken place. In any instances where she could offer information, she was usually able to remember clearly that she had been told the information in question and when pressed she would consistently deny any spontaneous recollection of a past event. There was no firm evidence of any temporal gradient in her autobiographical memory loss. Examples of her autobiographical memory loss include the following.

Holidays. While she knew that she went on several holidays prior to her accident, she indicated that this was on the basis of what she had recently been told by her family. She could not recall any incident during recent holidays. For example, she had no memory for horse-riding during a holiday in Scotland in September 1988, a few months prior to the accident. On one occasion, she apparently did go horse-riding all day and was unable to walk properly for the whole of the next day. She had no personal memories for holidays in Majorca or Ibiza where she went in the years prior to her injury, nor could she recall being in Rhodes on a holiday in the 1970s. She could recall no holiday in her childhood (she apparently went as a child to Austria and the South of France with her parents).

Hospital treatment. She could not remember two hospital admissions as a child, one for ear surgery and the other for a burn, though she indicated that she was now aware of the latter episode as her parents had told her about this since the head injury.

Occupational history. She had worked as a nanny for the 8 yrs after leaving college. She was able to give the names of some parents for whom she had worked as a nanny, and of some of the children of whom she took care. However, her account of this pre-injury period was much less detailed than that which her fiancé could offer, and she was unable to describe any incident which had occurred during this period. When she recently saw some of the children again and saw one of the day nurseries in which she had worked, she indicated that she had some 'feelings' of familiarity and was aware that the children 'meant something' to her, but could not retrieve any identity or contextual information nor could she recall any particular memories associated with them. It thus appeared that this form of 'exposure priming' did not bring back specific episodic memories for past events.

Houses. She was able to give an accurate list of the places in which she had lived in the years prior to her injury, but she again stated that this was on the basis of what she had been told She had no memories for the places in which she had lived as a child or teenager.

Cars. She has no memories for particular pre-injury incidents which had occurred (such as a car radio being stolen, an exhaust falling off the car, etc.) in relation to the cars which she had driven. She has no memory of learning to drive a car.

Educational experience. She can recall the names of the college and schools she attended on the basis of what she has been told. To specific questioning she could only recall the names of teachers which she had recently been told by her family. She could give the name of the headmistress and a class teacher in her secondary school, as these had been told to her, but she could not recall the names of any other teachers or of any teachers in primary school. She could not give the names of her best friends in her primary school. She could give the names of two friends from secondary school, but again she had been told these since the accident.

Births. She has no memories for particular births of which she would have been aware during her time as a nanny, though she was able to give the name of her godson and of his mother.

Deaths. She has no memory of the death of her fiancé's father (which occurred 8 mths before the injury), though is aware of this on account of being told about it. She also could not recollect the funeral of one of her grandmothers, which she attended and which occurred about 4 yrs before the injury.

Weddings. She did not have any specific memories for three weddings which she attended in the 8 yrs prior to her injury

In summary, she had almost complete loss of memory for information and events relating to the period prior to her injury. It would seem that her 'personal semantic' memory was less severely affected than her memory for specific incidents and events which had taken place. There was no firm evidence of any temporal gradient in her autobiographical memory loss. So marked was the retrograde amnesia which L.T displayed that she was taken by her family to visit a number of the places associated with her autobiographical memory loss (in the hope that this might trigger her past memories), for example houses in which she had lived. She indicated that this 'exposure priming' did not bring back any significant memory related to the place in question. She did admit to some feeling of familiarity in respect of the place, but also indicated that since her family had shown her photographs of the places as well it was difficult for her to know how significant such feelings of familiarity were.

Within her dense retrograde amnesia, there was some sparing of certain forms of memory and these closely paralleled observations of sparing in the more common anterograde amnesias. Thus, L.T. could still perform perceptual-motor skills which she had acquired prior to her injury. She could play the piano and read music, and when asked to drive a car she was able to do this for a short distance without a need to be instructed in the component skills involved. However, she had no recollection at all of the original learning experiences, and, for example, could not recall her driving test. A further sparing in her retrograde amnesia is the observation by her and her fiancé that when she has met individuals from her past such as children she once looked after, she has an 'emotional' familiarity recognition of them, even though specific identity or contextual information did not come to hand.

In a corresponding interview for *post-injury events*, it was much easier for her to provide information. Thus, she was able to describe holidays which she had taken during the past year (including incidents which occurred during such holidays), her outpatient treatment, events relating to her house and car, and recent births in families whom she knew. In general, her memory for such events was as detailed as that provided by her fiancé.

A further assessment of L.T.'s autobiographical memory was carried out using a cued recall technique in which the patient has to offer a specific past memory in respect of a particular cue word. A similar procedure was followed to that previously reported (MacKinnon and Squire, 1989). Ten words were presented to L.T. one at a time (tree, nail, baby, ticket, bottle, flag, book, window, street, picture). The test was carried out twice, with a 15 min gap between sessions and with the instructions to recall either pre-injury events or post-injury events. Responses were recorded verbatim. L.T. was given the following instructions: 'I will say a word to you, and I'd like you to try to recall an event from before/after your head injury that could be associated with the word. You can select an episode from any time before/after your injury, but try to choose one that you can remember as having happened at a particular time and in a particular place.' In both sessions, L.T. was encouraged by probes to offer specific time/place information in respect of a particular event. L.T.'s responses were rated by a clinical neuropsychologist who was 'blind' to the case, and who was told that the set of responses could have come from a neurological or a control patient. A rating of 0–3 was given according to the amount of detail (3 = maximum amount of detail) which was provided by L.T. in her verbal report. Note the dramatic difference between the two sets of test scores, even though the pre-injury period covers most of her life, whereas the post-injury period only covers around 20 mths. L.T.'s performance for pre-injury and post-injury events is indicated in Fig. 2, which shows zero recall for pre-injury memories and a much higher score for post-injury memories.

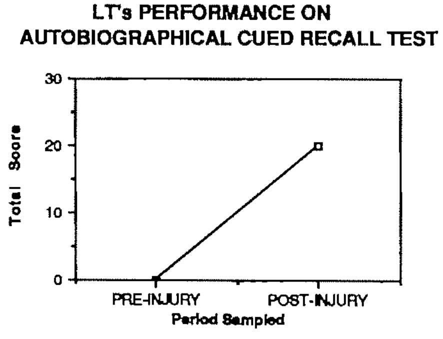

FIG. 2. L.T.'s performance on the autobiographical cued recall test

Retrograde memory assessment: memory for public events

L.T. was tested on a range of remote memory tests: (1) identification of famous scenes (Kopelman, 1989); (2) the dead/alive test (Kapur *et al.*, 1989) which assesses memory for personalities who had been famous over the past 30 yrs; (3) a test of memory for famous faces (Montaldi and Parkin, 189); (4) a test of memory for famous names.

Identification of famous scenes. The famous scenes test assessed recall and recognition for news events which took place over the past 50 yrs but only post-1975 items were considered in view of L.T.'s age. Items were presented on slides, with no specific time-limit for a response. L.T.'s performance and that of four control subjects on the recall and recognition parts of post-1975 test items is shown in Fig. 3. As can be seen, L.T. was markedly impaired on the recall portion, with a milder impairment on recognition testing. There was no evidence of any temporal gradient in her memory performance.

Dead/alive test. The dead/alive memory test assessed L.T.'s ability to indicate whether a famous personality from the past was dead or alive, whether he/she had been killed or had died of natural causes, and an indication of the time period (in 5-yr bands) when he/she died. Forty items made up the test: 30 related to famous personalities who had died, and the remaining 10 referred to people who were still living. L.T. and a group of four matched control subjects were tested. Items were scored such that for the 'alive' items, subjects obtained a score of two or zero. If they correctly indicated that a personality had died, they were given two points. A further two points were awarded if they could indicate the nature of the death (killed/natural causes), and an additional two points were allocated if the time period of the death was within one band-width of the time of death. For example, if the person had died in 1963, the subject would obtain two points if she indicated the bandwidths 1955–1959, 1960–1964 or 1965–1969. Figure 4 shows L.T.'s performance and that of control subjects for 'dead' and for 'alive' items. As can be seen, L.T. showed markedly impaired performance for items from all the decades, and her deficit extended both to personalities who were dead and those who were alive.

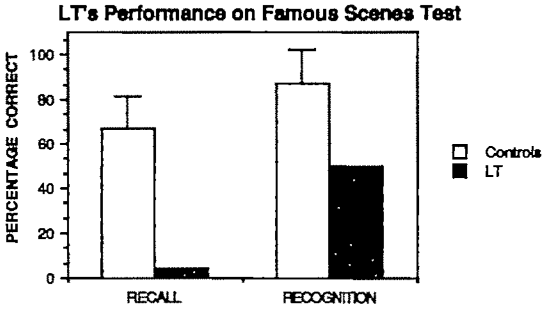

FIG. 3. L.T.'s performance on famous scenes test. L.T. and four matched control subjects were shown 22 famous scenes dating from 1975 to 1988 They were asked to identify the scene (recall), and were also given a forced-choice recognition test for the item (recognition). Standard deviation values are represented as bars.

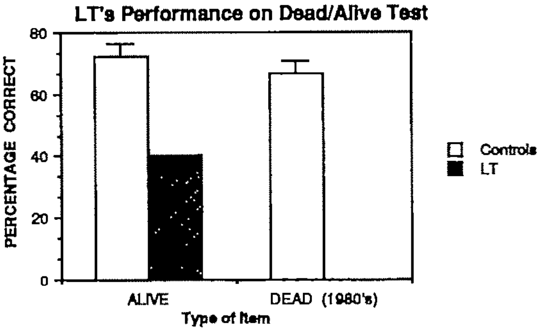

FIG. 4 L T.'s performance on dead/alive test of retrograde amnesia. L T and four matched control subjects had to indicate whether a famous personality was dead or alive, how they died (natural causes or killed) and when they died (in 5-yr bands). For further details on test construction and scoring, *see* Kapur *et al.* (1989) Items are grouped according to decade, and performance on items from the 1980s is shown Standard deviation values are represented as bars As can be seen, L.T scored at zero level for the 'dead' items.

Memory for famous faces. L T. was also given a retrograde amnesia test (Montaldi and Parkin, 1989) in which famous faces from earlier decades (1936–1985) had to be identified. Five decades were sampled: 1936–1945, 1946–1955, 1956–1965, 1966–1975, 1976–1985, with six items per decade. Two conditions were tested, one where the individuals were shown out of context and the other where the individuals were shown in a context which closely related to their occupation (e.g a famous tennis player in an evening dress or in action wearing tennis gear). L.T.'s performance on this test, together with that of a group of four matched control subjects is shown in Fig. 5. As can be seen, L.T. performed poorly on the test. She showed little if any improvement in the 'context' compared with the 'no context' condition.

Memory for famous names. L.T. was shown a set of 48 names, 23 of which had been famous over the past 15 yrs. In most instances, these were names which had been famous for a short period (e.g. Bobby Sands) and had then faded out of the news. L.T. was asked to indicate whether the name was that of someone who had been in the news, and if so to indicate what they had been famous for As can be seen from Fig. 6, L.T.'s score on this test was much lower than that of control subjects She was only able to indicate as familiar 39% of the target items, and was only able to give identifiable information for three of the names. She made no false positive responses to distractor items, and the number of her correct responses was too small to permit statements as to the presence/absence of any temporal gradient in her remote memory loss.

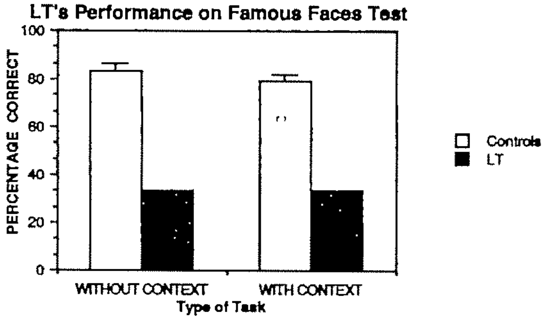

FIG. 5 L.T.'s performance on a famous faces test of retrograde amnesia. Faces were shown in their natural context, or out of context, and L T. and four matched control subjects had to name the famous face. Faces were firstly shown out of context, and after a few minutes shown in their natural context This figure shows performance in respect of famous faces dating from the mid-1970s to the mid-1980s. Standard deviation values are represented as bars

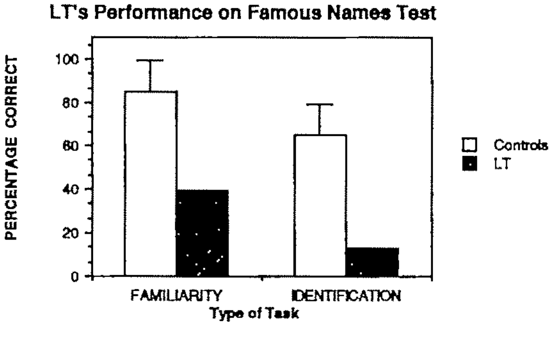

FIG 6 L.T.'s performance on famous names test of retrograde amnesia. Twenty-three famous names, relating to personalities who were famous in the period 1975–1988, were presented along with 25 distractor names L T and five matched control subjects had to indicate whether the name was that of a famous personality (familiarity recognition), and to indicate for what the person was famous (identification) Standard deviation values are represented as bars.

DISCUSSION

Our patient, L.T., who suffered a severe closed head injury, was left with a dense retrograde amnesia, but she showed only limited anterograde memory loss. Her retrograde amnesia included both public events and autobiographical material, and her memory loss for personal past events extended back to her childhood. Magnetic resonance scanning revealed focal pathology in the anterior portion of both temporal lobes, with predominantly lateral rather than medial temporal lobe involvement. Some additional, much more limited pathology was present in the medial undersurface of both frontal poles.

Our findings highlight the independence of anterograde and retrograde memory mechanisms, and substantiate evidence from patients with global amnesia (Squire *et al.*, 1989). At the level of ictal memory loss, our data also parallel observations made regarding the dissociations which occur between the presence of pre-traumatic and post-traumatic amnesia (Teuber, 1969; Russell, 1971).

The pattern of memory loss shown by L.T. was quite similar to that reported by Goldberg *et al.* (1981), and the aetiology of our patient's pathology was the same. Although Goldberg *et al.* (1981) emphasized the mesencephalic lesion evident on their patient's CT scan, it is worth noting that their set of CT findings also included 'moderate ventricular enlargement, a region of rarefaction in the right middle and posterior temporal areas, and a small region of rarefaction along the left mid-temporal convexity' (p. 1932). Our patient's MR scan showed mild ventricular dilatation, and major pathology in both anterior temporal lobes. We were unable to detect a mid-brain lesion of the type seen by Goldberg *et al.* (1981) and in view of the large number of axial, sagittal and coronal slices gathered in the various CT and MR examinations, it is unlikely that such a lesion could have been missed by our imaging procedures.

The frontal lobe pathology which was present on L.T.'s MR scan may have played a part in her remote memory loss, though this is unlikely in view of the limited extent of the lesion. While there is some evidence to implicate frontal lobe pathology in retrograde amnesia (Kopelman, 1989), other data suggest that frontal lobe damage does not play a critical role in autobiographical memory loss (Dall'Ora *et al.*, 1989). We favour a hypothesis which puts primary weight on the bilateral temporal lobe lesions which were present. Such pathology is invariably present in patients with amnesia following herpes encephalitis, and is probably also present in some patients with an Alzheimer-type dementia. These patients usually suffer from hippocampal and related medial temporal lobe pathology, as well as damage both to other temporal lobe neocortical structures, and to other cortical regions, making it difficult to confirm or refute precise anatomical hypotheses from such patients alone. However, we broadly support the conclusions reached by Van Hoesen (1990), who concluded on the basis of the locus of Alzheimer pathology that 'changes that affect the lateral temporal, posterior parahippocampal, temporopolar, and anterior insular cortices further exacerbate the problem and contribute to retrograde memory abnormalities in the episodic and contextual memory realms' (p. 254). Van Hoesen also highlighted the multi-modal nature of afferent connections to these structures from association cortices, and we would argue that many components of retrograde memory, in particular autobiographical knowledge, are invariably multi-modal in nature.

Impaired performance on retrograde memory tasks has also been reported in patients with combined left-anterior medial and lateral temporal ablation (Barr *et al.*,, 1990), but this pattern of memory loss differed from that shown by L.T. in that her autobiographical memory loss was much more severe, and the degree of anterograde memory deficit was both less marked and less extensive. For example, in the patients with left temporal ablation, delayed story recall was worse than immediate recall, and delayed recall of a complex design was markedly impaired. In the case of L.T., her delayed story recall, though below average, was in fact slightly better than her immediate recall, and her delayed recall of complex figures from the Wechsler Memory Scale was above average. It is quite possible that it is the bilateral nature of our patient's pathology which underlies her dense autobiographical memory loss, since sparing of this domain of memory functioning has been reported in patients with primarily unilateral left medial temporal pathology (De Renzi *et al.*, 1987) or left parietal pathology (Grossi *et al.*, 1988), who otherwise also had extensive memory deficits for past public events.

In our patient, the hippocampus was considered on close examination to be intact. Patients with focal hippocampal pathology have been found to have minimal retrograde amnesia (Zola-Morgan *et al.*, 1986). The degree of retrograde amnesia in the patient H.M. has been variably reported to be from a few years (Marslen-Wilson and Teuber, 1975; Gabrieli *et al.*, 1988) to around 11 yrs (Corkin, 1984). As Corkin (1984) has pointed out, the true extent of his retrograde amnesia is probably difficult to know with certainty in view of the length of time since the onset of his amnesia and the fact that his learning capacity was probably not perfect prior to his surgery because of his severe epilepsy and the high doses of anti-convulsant medication he had been receiving. Nevertheless, if one accepts that H.M.'s retrograde amnesia is rather mild this can be explained, in the context of the findings from the present study, by the relative absence of lateral neocortical temporal lobe damage in the pattern of lesions which he sustained. H.M.'s surgery entailed an excision which 'extended posteriorly from the midpoint of the medial top of the temporal lobes for a distance of roughly 8 cm. In this fashion, the prepyriform gyrus, uncus, amygdala, hippocampus, and hippocampal gyrus were resected bilaterally. The removal was limited superiorly and laterally by the temporal horns, and extended approximately 3 cm posterior to the medial portion of the petrous ridge' (Scoville, 1968, pp. 211–212; *see also* Corkin, 1984 for CT confirmation of the extent of surgery). Thus, the lateral portions of the anterior and mid regions of the temporal lobes were spared by this surgery, and we would hypothesize that these structures, which were specifically lesioned in our patient L.T., may be the critical ones that determine the extent and severity of retrograde amnesia. Patients who have undergone ablation of both lateral and medial temporal lobe structures have seldom been reported, though in one such study (Terzian and Dalle Ore, 1955) there was clinical evidence in the early post-surgical period of a dense anterograde and retrograde amnesia. Where there is bilateral hippocampal damage, but sparing of the neocortex of one temporal lobe, as in Case 1 reported by Penfield and Mathieson (1974), there is evidence for recovery of an initially marked retrograde amnesia together with persistence of anterograde memory loss. Cases where bilateral temporal lobe ablation completely spares medial temporal lobe regions are also rare, and have seldom been studied in detail, though in a short case report of one patient (Petit-Dutaillis *et al.*, 1954) there was clinical evidence for a residual degree of retrograde amnesia with substantial recovery of an initial anterograde amnesia. Since our case was one of blunt head injury, it remains possible that some additional focal or diffuse pathology was present which could not be visualized by magnetic resonance imaging. Further studies of this type, examining groups of patients with a traumatic or non-traumatic aetiology, should shed further light on the critical nature of the lesions which we found in our patient.

In conclusion, our observations demonstrate the independence of anterograde and retrograde memory mechanisms, and point to structures and pathways in the anterior temporal lobes as playing a critical role in memory for past events.

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NEUROPSYCHOLOGICAL AND NEUROANATOMICAL DIMENSIONS OF IDEOMOTOR APRAXIA

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SUMMARY

Fifty-five right-handed men with left hemisphere stroke were systematically investigated for ideomotor apraxia of various body parts. Standardized aphasia and apraxia examinations in all cases, and appropriately timed CT in 28 cases, were used for analysis of psychological and anatomical properties of ideomotor apraxia. It is not possible to ignore the modality of eliciting the movement (command or imitation) and the body part being moved (buccofacial, limb or whole body) from any comprehensive theory about ideomotor apraxia. Different levels of performance are seen with different body parts to different modalities in different aphasic groups. Some subtypes of ideomotor apraxia (buccofacial) have highly specified anatomical basis. Some (limb) have apparently distributed anatomies, and others (whole body) have as yet unknown bases.

INTRODUCTION

The first systematic analysis of apraxia was performed by Liepmann (1900, 1906, 1908) and Liepmann and Maas (1907). The terminology and conceptual framework for the apraxic disorders arose from those studies, and both the terminology and the theoretical concepts that it captures remain in use today. The disorder that Liepmann called ideomotor apraxia has been the primary focus of subsequent research. All investigations, including Liepmann's, of ideomotor apraxia have observed a close relationship between apraxia and aphasia. Much analysis of apraxia even today seems motivated by hypotheses about the nature of this relationship.

Despite pervasive adherence to Liepmann's schemata (Goodglass and Kaplan, 1963; Geschwind, 1965, 1975; De Renzi *et al.*, 1966, 1980; Heilman *et al.*, 1982; Kertesz and Hooper, 1982; Lehmkuhl *et al.*, 1983) and general, but not complete agreement (Kimura and Archibald, 1974; Kimura, 1977, 1982; Mateer and Kimura, 1977; Watson and Kimura, 1989) that interpretation of at least some of the clinical manifestations of ideomotor apraxia is contaminated by a co-occurring aphasia, a century of research and description has left a number of unresolved questions about ideomotor apraxia. It is not known with certainty if the nature or severity of ideomotor apraxia depend upon the stimulus used to elicit it. This question has often been simply subsumed in a methodological compromise, using imitation to circumvent poor comprehension. The precise relationships between several speech and language deficits and the phenomenology

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of apraxia are not established although numerous aspects of this relationship have been investigated. The range of motor systems (body parts) that can be involved in ideomotor apraxia has often not been specified. If ideomotor apraxia can involve buccofacial or axial movements as well as limb, then other potential issues arise, such as, the effects of different lesion sites on ideomotor apraxia of different body parts or preferential sparing of different body parts.

There is not a universally accepted, empirically supported unique definition of ideomotor apraxia. All definitions in current use incorporate one or more claims about the nature of ideomotor apraxia that are not completely accepted. There is, however, a thread of general agreement [except Kimura *et al.* (Kimura and Archibald, 1974; Kimura, 1977, 1982; Mateer and Kimura, 1977; Watson and Kimura, 1989)] around which the definition of ideomotor apraxia for this report was constructed. Ideomotor apraxia is a disorder of 'learned movements' (Geschwind, 1975) or 'skilled movements' without meaning explicitly symbolic movements (Heilman *et al.*, 1982). Ideomotor apraxia cannot be accounted for by any elemental neurological or motivational deficit. It may be most reliably demonstrated either by command (Geschwind, 1975) or by imitation (De Renzi *et al.*, 1980), the former more closely matching the naturalistic setting in which movement is elicited, but the later neutralizing any limitations in language comprehension.

We report the results of an investigation of ideomotor apraxia in 55 patients with left hemisphere damage. The investigation was designed to explore three separate, but often entangled, issues: (1) the effect of modality of request, command or imitation, on praxis performance; (2) the relationship between ideomotor apraxia and aphasia, either overall aphasia syndrome or individual components of disordered language; (3) the lesion correlations of apraxic performances of each testable motor subsystem (face, limb, axial, etc.).

SUBJECTS AND METHODS

Subjects

Consecutive patients hospitalized for left hemisphere ischaemic stroke were evaluated. All right-handed patients with no prior clinical history of stroke were included, except for very impaired patients who could not be instructed or even modelled into the appropriate set for praxis testing All patients were male; age and education information are summarized in Table 1.

Controls

Two control groups were utilized. A group of 23 normal right-handed men matched to the main age cohort of the patient group (45–75) was tested. A group of unilateral right hemisphere ischaemic stroke cases was also tested. This group was also all right-handed men with no history of stroke prior to the index event, distributed across the main age cohort of the left hemisphere-damaged group. Age and educational data for both control groups is summarized in Table 1.

For both groups of stroke patients all evaluations were performed between the third and the twelfth week after onset of stroke. Patients were tested as close to the third week post-onset as possible.

Aphasia assessment

Language was evaluated with the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass and Kaplan, 1983) by experienced speech pathologists unaware of any aspect of the apraxia project. Aphasia diagnoses met the criteria outlined by Goodglass and Kaplan (1983) Four groupings of BDAE subtests were used

TABLE 1 CASES AND CONTROLS. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Aphasics	*n*	*Age (yrs)*	*Education (yrs)*	*TPO (wks)*	*HP*	*HH*	*COMP*
Transcortical Motor	10	57.9 (49–62)	11.8 (10–16)	5.4 (2–11)	2	0	+0.50
Broca's	13	60.77 (52–73)	11.25 (7–16)	5.46 (3–12)	4	0	+0.18
Global	8	52.75 (31–72)	12.14 (8–16)	6.5 (3–10)	6	6	−1.40
Conduction	6	60.17 (48–72)	11.67 (11–12)	3.83 (3–6)	1	2	+0.75
Wernicke's	9	6.61 (57–78)	10.63 (8–12)	6.67 (3–10)	1	8	−1.03
Anomic	8	59.13 (48–70)	9.25 (7–12)	5.13 (2–10)	2	4	+0.56
Right brain Damaged	18	56.28 (24–77)	10.94 (8–14)	5.44 (3–13)	12	7	—
Normals	23	60.00 (47–79)	12.48 (7–16)	—	—	—	—

TPO = time post-onset to initial testing, HP = number of cases with limiting hemiparesis, HH = number of cases with significant visual field deficit, COMP = overall auditory comprehension on BDAE as mean of group z-scores.

for statistical studies: articulatory agility; repetition of sentences; overall auditory comprehension; overall severity.

Apraxia assessment

Apraxia testing was carried out by one of two examiners. The test items and their division by body parts are indicated in the Appendix. Between representational and non-representational tasks, there was as much correspondence of motor complexity as could be devised. For example, touch your nose (non-representational), salute (simple intransitive posture), wipe sweat off of your forehead (simple transitive movement without an object), and pretend to tip your hat (complex transitive movement requiring pretended object use) all demanded bringing the hand to the upper face. This correspondence was maintained as much as possible for all body parts.

After presentation of the complete battery to command, there was a rest break, and the entire battery was presented to imitation. The order of modality (imitation or command) was held constant because of concern that imitation would provide a model which might facilitate even a slightly delayed presentation of the task to command.

The order of presentation of body parts was counterbalanced across subjects. In the command mode, the patient was instructed to carry out the movement that he heard requested. In the imitation mode, the patient was told to make exactly the same movement that the examiner made. Before each body part grouping, the patient was told which body part was about to be tested and lightly touched in the appropriate area. If no movement was made by the patient, the request (or the gesture) was repeated once. No repetitions were allowed for an incorrect response, only for no response. If after repetition the patient still made no response, the test moved to the next item.

Scoring of apraxia

The scoring scale was based on qualitative differences in performance observed in the developmental acquisition of praxis in childhood (Kaplan, 1968). Performance was scored from no response to completely correct response (*see* Table 2). For each body part to each modality of request there were 8 to 12 trial items. The scores given are the means across the trials. Whenever the neurologic condition permitted, both the right and the left arm were tested to both modalities.

Inter-rater reliability was assessed. For 10 patients, the two raters simultaneously but independently scored the same test sessions. For overall agreement, for agreement on each body part and for agreement for each modality, the reliability of rating was 91%.

TABLE 2 SCORING OF PRAXIS

Score	*Achievement*
5	Completely correct
4	Correct but only after a self cue or after one or more incorrect movements or with verbalization which directs the movement.
3	For buccofacial and respiratory: onomatopoetic or substituted verbalization
	For limb: body part as object or spatial error such as incorrect spacing, rotation or precise limb placement
	For axial appropriate limb movements without axial movement
2	Repeated undifferentiated movements of correct body part
1	Perseveration.
0	No movement

CT studies

Non-enhanced CT scans were performed from 2 to 12 wks after onset. Scans were evaluated by two experienced CT researchers who were blind to the apraxia study methodology or hypotheses. The raters used a neuroanatomical checklist (Fig. 1) and rating methodology based on prior research at our unit (Naeser *et al.*, 1990). This method captures partial damage to a rated region. Scan inclinations were determined before lesion ratings were made. A CT atlas (Matsui and Hirano, 1978) was utilized to clarify cortical locations for CTs in anomalous inclinations. For anatomically coherent areas present on more than one CT slice (lower motor cortex, head of caudate nucleus, etc.), the scores for the individual CT slices were summed. For statistical analyses, all scores were rectified to percentage of area with lesion. Only cases with unequivocal single lesions demonstrated in the post-acute interval after 3 wks post-onset were included for anatomical analyses. Not all patients in the praxis studies above had an adequate CT, and others had small (and clinically silent) lesions in addition to the one producing the acute presentation to the hospital. In both events, the cases were included in the praxis study but not the CT lesion analysis.

RESULTS

Normals

Many normals made occasional, minor errors on praxis tests to command. Means and standard deviations for the 23 normals to command are shown in Table 3. A cut-off for normal performance was taken as the mean for each body part minus two standard deviations. Normals perform better on these tasks of gesture when given a model to imitate. To imitation, there were very few errors. No normal made more than one error, so we considered any performance with more than one error to be apraxic.

Right hemisphere stroke controls

Mean performance to command and to imitation did not differ from the normals. There was some difficulty in this group with one task from the buccofacial tasks; the single command to frown as if angry was incorrectly performed in 13 of the 18 patients.

Left hemisphere stroke cases

Aphasia group × body part × modality × representationality. Two separate mixed design analyses of variance (ANOVA) were used to assess whether apraxia scores were related to the factors of aphasia type (6 levels), body part (4 levels), modality of presentation (2 levels) or representationality of movement (2 levels, with all of the representational movements for limbs collapsed into one group). The results of the ANOVA are

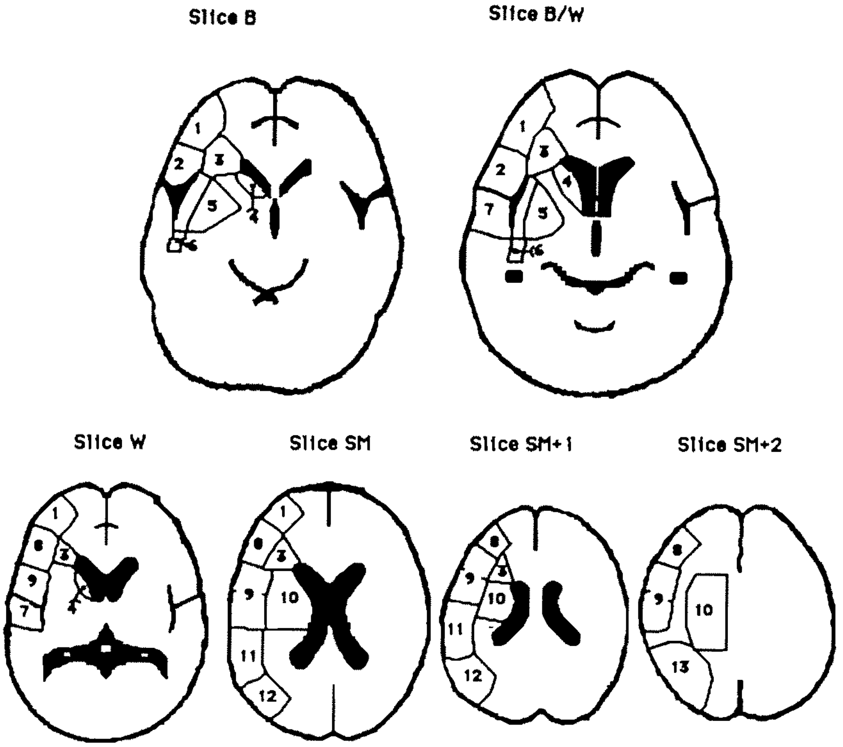

FIG. 1. Schematic representation of brain regions rated for lesion site studies. Numbers refer to regions listed in Tables 5A,B.

TABLE 3 APRAXIA SCORES FOR 23 NORMALS, THRESHOLDS FOR ABNORMAL PERFORMANCE TO COMMAND

	Buccofacial	*Respiratory*	*Limb*	*Axial*
Mean (max. score 5)	4.88	4.62	4.96	4.98
Standard deviation	0.28	0.42	0.12	0.06
Lower limit (mean −2×SD)	4.32	3.78	4.73	4.86

summarized in Table 4. All pair-wise comparisons of means were carried out using Newman-Keuls *post hoc* procedure. Significant effects were found for aphasia group, modality of presentation, body part tested and representationality.

The conduction aphasic and the anomic aphasic *groups* were not significantly apraxic when compared with the normal controls. The other 4 groups were significantly apraxic. Some of the effects of aphasia group are displayed in Fig. 2. Global aphasics were significantly more apraxic than the other groups on all body parts and to both modalities. Wernicke's aphasics were significantly more apraxic than transcortical motor aphasics and Broca's aphasics to command, but the differences disappeared to imitation. To imitation, in fact, the Wernicke's group was significantly less apraxic than the Broca's aphasics on the oral and respiratory tasks.

TABLE 4 RESULTS OF ANOVAs OF APRAXIA, APHASIC GROUPS WITH APRAXIA SCORE BY BODY PART AS DEPENDENT MEASURE

SV	*df*	*MS*	*F*	*P*
Anova table—modality				
Group	6	46.43	11.63	<0.001
Modality	1	57.92	43.39	<0.001
Body part	3	20.54	29.69	<0.001
Group × modality	6	3.01	2.53	<0.05
Group × body part	18	1.42	2.06	<0.01
Modality × body part	3	0.54	2.39	<0.07
Group × modality × body part	18	0.38	1.64	<0.06
Anova table—representationality				
Group	6	55.76	11.46	<0.001
Representationality (R)	1	14.98	22.66	<0.001
Body part	3	23.24	32.88	<0.001
Group × R	6	0.73	1.1	NS
Group × body part	18	1.00	1.41	NS
R × body part	3	0.95	2.7	<0.05
Group × R × body part	18	0.23	0.66	NS

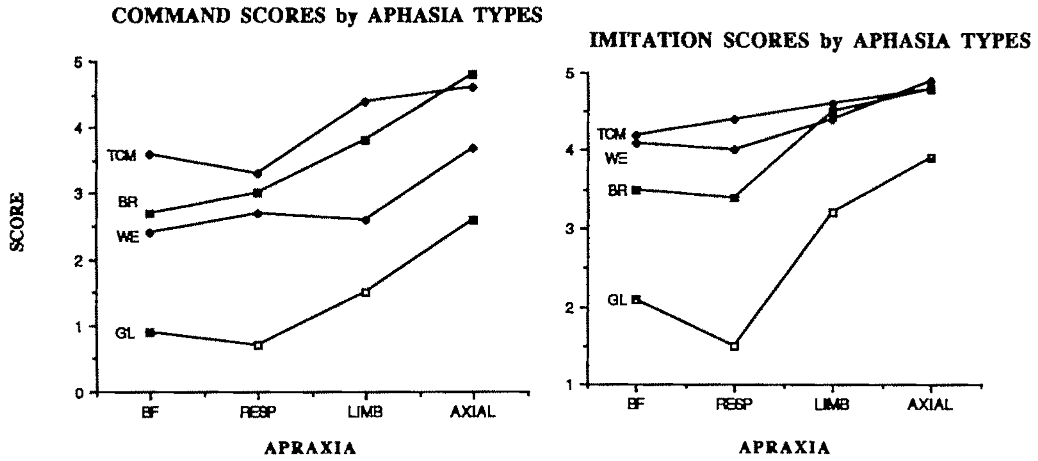

FIG 2. Group means for each body part to each modality for the aphasic groups. Conduction and anomic aphasics did not differ from normal controls.

The effects of representationality across and within aphasic groups are demonstrated in Table 4. In the apraxic subgroups, there are 16 possible comparisons of representationality and non-representationality—4 aphasic, apraxic groups, 2 modalities of presentation and 2 levels of representationality. The overall effect of representationality is strong (F = 22.66, df = 1; *P* < 0.001). In 15 comparisons, the non-representational movements were better performed than matched representational movements, although variability in the groups precluded demonstration of a significant group × body part effect for representationality.

Some of the effects of body part within aphasic groups to command can be seen in Fig. 2 and in Table 4. The main effect of body part is strong (F = 20.54, df = 3,

$P < 0.001$). Axial movements are significantly better performed *to command* than are all other body parts for all aphasic, apraxic groups, except the transcortical motor group. Limb movements are significantly better performed to command than buccofacial and respiratory in Broca's aphasia, transcortical motor aphasia and global aphasia. Note that these different effects across body parts *to command* are seen in groups with poor auditory comprehension (Wernicke's aphasia and global aphasia) as well as in groups with good auditory comprehension.

The significant effects ($F = 57.92$, df = 1, $P < 0.001$) of modality within aphasia subgroups can be seen in Fig. 2 and Table 4. All body parts except those near a ceiling effect (limb and axial for Broca's and transcortical motor aphasia groups) were significantly better to imitation than command. Even for the patients with good comprehension, there was still a significant improvement to imitation in the categories that did not already approach a normal ceiling to command. In the patient groups with poor auditory comprehension, all 8 categories improved significantly to imitation.

A subsequent two-way repeated measures ANOVA was performed on 16 anterior cases without significant hemiparesis to assess whether limb apraxia (dependent measure) was related to the arm used (2 levels: left or right arm) or to representationality (all 4 levels). There were no significant effects of left versus right arm at any level of representationality; there was not even any trend toward the left arm being more impaired in this group with anterior/central lesions. Cases were individually inspected; there were no cases with significantly more apraxia of the left arm. For either arm, the trend was uniformly toward lower scores for increasingly representational tasks, but none of the differences reached significance.

Correlations with language deficits. Pearson Product Moment linear correlation coefficients were calculated for the cases with anterior lesions (transcortical motor aphasia, Broca's aphasia, and anomic aphasics with anterior lesions). Apraxia scores for each body part were used as the criterion variable in each calculation. For anterior cases, language variables were overall aphasia severity, sentence repetition and articulatory agility. Only overall aphasia severity correlated significantly ($P < 0.05$) with any of the apraxia scores: buccofacial to command, $r = 0.53$, buccofacial to imitation, $r = 0.51$, respiratory to imitation, $r = 0.59$.

A separate correlation was calculated for cases with poor comprehension (globals and Wernicke's). The predictor language variables used for the analysis were overall aphasia severity, repetition and auditory comprehension. Not surprisingly, every body part performance to command had a significant correlation ($P < 0.05$) with comprehension: buccofacial $r = 0.503$ ($P < 0.04$), respiratory $r = 0.65$ ($P < 0.005$), limb $r = 0.71$ ($P < 0.002$), axial $R = 0.66$ ($P < 0.004$). Even for praxis to imitation, however, there was a significant correlation with auditory comprehension for respiratory ($r = 0.555$; $P < 0.03$) and axial ($r = 0.595$; $P < 0.02$) movements and borderline significant correlation of buccofacial ($r = 0.441$; $P < 0.077$).

Anatomical-apraxia relationships. A set of criteria for an unequivocally apraxic performance was established. For each body part, the normal controls were analysed; a score lower than two standard deviations below the mean for normals defined the criterion for apraxia. For each body part of each patient, performance was dichotomized as apraxic or not. The same metric was used independently for tasks to command and to imitation.

Because there was virtually no overlap between lesion sites in the anterior and posterior cases, yet both included patients with apraxia, the two groups were analysed separately. All patients with anterior or central (rolandic) lesions on CT were clustered for one analysis. (These cases came from the diagnostic categories of Broca's, transcortical motor and anomic aphasics.) All patients with posterior lesions were clustered for a separate analysis. (These cases came from the diagnostic categories of Wernicke's conduction and anomic aphasics.) Cases with global aphasia were excluded from the lesion analysis. All patients with global aphasia were severely apraxic, rendering it impossible to differentiate a critical lesion for apraxia. The CT lesion scores were collapsed to reflect anatomically coherent regions as a method to reduce the number of CT variables. Table 5A,B summarizes the regions that were utilized for each analysis.

Separate sets of stepwise discriminant analyses were carried out for aphasics with anterior/central lesions ($n = 15$) and for aphasics with posterior lesions ($n = 13$). For each body part and modality combination, subjects were categorized into two groups: apraxic or not apraxic. This yielded a total of 16 discriminant analyses, eight for each anatomical grouping.

For anterior/central cases to command, the discriminant analysis identified a significant relationship between lesions involving both the motor association cortex (including Broca's area) and the anterior two-thirds of the paraventricular white matter with both

TABLE 5A. BRAIN REGIONS RATED FOR ANTERIOR AND CENTRAL CASES

Rolandic cortex: all lesion in the prerolandic and postrolandic gyri from the sylvian fissure to the highest CT slice (9).

Motor association cortex:
- (*a*) All lesion in Broca's area, i.e. the opercular and triangular gyri (2).
- (*b*) Dorsolateral frontal lobe anterior to the prerolandic gyrus at CT slices above Broca's area (8).

Frontal premotor cortex (1).

The white matter deep to rolandic cortex and motor association cortex including the anterior two-thirds of the paraventricular white matter (10).

The inferior parietal lobule including the anterior supramarginal gyrus (11)

Deep structures:
- (*a*) The most anterior paraventricular white matter around and above the frontal horn (3).
- (*b*) Head of caudate nucleus (4).
- (*c*) Putamen (5).

Numbers in parentheses identify areas on Fig. 1

TABLE 5B BRAIN REGIONS RATED FOR POSTERIOR CASES

Rolandic cortex: all lesions in the prerolandic and postrolandic gyri from the sylvian fissure to the highest CT slice (9).

Inferior parietal lobule including.
- (*a*) Supramarginal gyrus (11).
- (*b*) Angular gyrus (12).

Superior temporal gyrus (7).

The white matter deep to rolandic cortex and inferior parietal cortex including the anterior two-thirds of the paraventricular white matter (10).

The temporal isthmus (6).

The superior parietal lobule (13).

Numbers in parentheses identify areas on Fig. 1.

buccofacial and respiratory apraxia. There were two cases who were apraxic without lesions in those areas; both had exclusively subcortical lesions (striatum, anterior limb internal capsule and anterior paraventricular white matter). There was no lesion configuration which produced a significant correlation with limb apraxia. Axial apraxia was also significantly associated with lesions in motor association cortex and paraventricular white matter, but *only if there was not* a lesion in the lower motor cortex.

For anterior/central cases to imitation, the discriminant analysis had only one significant sort, perhaps as a ceiling effect as many fewer anterior cases were apraxic to imitation.

For posterior cases to command, there were only two significant sorts. Simultaneous lesions in the anterior two-thirds of the paraventricular white matter and the temporal isthmus correctly predicted buccofacial (but not respiratory) apraxia in 85% of the cases. Lesion in the temporal isthmus successfully predicted axial apraxia in 77% of the cases. For posterior cases to imitation, there were no significant associations between anatomy and apraxia. A ceiling effect is even likelier in this group.

Summary of the results

Effect of modality. Performance to imitation was always significantly better than to command even in those patients with good auditory comprehension. In patients with poor auditory comprehension, the improvement to imitation was across all body parts.

Relationship between apraxia and overall aphasia diagnosis. The conduction aphasic and the anomic aphasic groups were not significantly apraxic although there were individual members of the groups who were mildly apraxic. When comprehension was accounted for, the Wernicke's aphasics were also arguably not apraxic. All other aphasia groups were apraxic. Patients with Broca's aphasia were more apraxic than patients with transcortical motor aphasia; this difference was more marked to command than to imitation although *failure to comprehend commands was not an issue with either group.* Broca's aphasics were particularly more impaired for buccofacial/respiratory movements. Patients with global aphasia were the most apraxic, whatever body part was tested or modality was used.

Anatomical correlates of apraxia for each body part. (*a*) Lesions in the deep anterior two-thirds of the paraventricular white matter were most commonly associated with ideomotor apraxia. The combination of lesion in the motor association cortex and lesion in that paraventricular white matter was strongly associated with buccofacial and respiratory apraxia in anterior aphasics (all with good comprehension); (*b*) buccofacial and respiratory movements are very similarly affected in aphasic, apraxic patients, and the critical anatomy for buccofacial and respiratory apraxia seems to be identical. There may be no important dissociations between them; (*c*) no single CT profile was uniquely correlated with limb apraxia; (*d*) axial movements (as defined for this investigation) are significantly better performed to command than all other body part movements in aphasic, apraxic patients. The relative preservation of axial movements in anterior/central cases may demand the apparent paradox of *more* damage to left hemisphere motor systems once the critical regions of motor association cortex and paraventricular white matter have been damaged. Relative preservation of axial movements in posterior cases may require the absence of damage to deep temporal lobe pathways.

Overall conclusions. Ideomotor apraxia is a multidimensional disorder involving different sensory-motor connections (modality of elicitation), different motor programs (body part utilized), different conceptual representations (meaningfulness) and different anatomies for the various interactions of body part and modality.

DISCUSSION

An extensive literature exists on the relationship between aphasia and ideomotor apraxia. It is difficult, however, to compare precisely our conclusions with the findings of prior investigators. This is due, in part, to different investigations having much different or more highly focused aims. The main reason that a comparison to our findings, or even a comprehensive summary of the literature is so difficult is that various investigators have made such different decisions about methodology. In addition, only a few prior studies were restricted to cases of stroke (Basso *et al.*, 1987*a*). In most studies the time post-onset was not controlled. Using different types of neuropathological processes and not allowing for the natural evolution of neuropsychological deficits might both influence findings (Basso *et al.*, 1987*a*).

Some investigations have analysed each body part separately (Goodglass and Kaplan, 1963; De Renzi *et al.*, 1966, 1980; Basso *et al.*, 1987*b*); others have lumped them into a composite (Kertesz and Hooper, 1982). Some investigators have not controlled modality of elicitation using case-by-case mixtures of command and imitation to elicit the optimal performance (Goodglass and Kaplan, 1963; Heilman *et al.*, 1982; Kertesz and Hooper, 1982). Others have restricted analysis to performance to imitation attempting to neutralize effects of variably impaired auditory comprehension (De Renzi *et al.*, 1966, 1980), although there could be variably impaired comprehension of gesture as well. There are potentially important differences in the types of movements tested, from so-called meaningless to meaningful to complex pantomime. Aphasia as a variable in these investigations is more similarly handled; patients are usually grouped by conventional aphasia diagnosis and then reanalysed with *post hoc* correlations to some measure of overall severity. Scoring methodologies also vary dramatically. Table 6 provides a summary of the methodologic variables in the most commonly cited reports.

In the current report, some of these methodologic differences have been controlled. Only ischaemic stroke cases were studied. All cases were studied in the post-acute epoch in which brain-behaviour correlations may be most robust. Other variables will be individually analysed in relationship to the existing literature.

Modality

The commonly used modalities of elicitation were independently explored in this report. In all groups and for all body parts, performance to imitation was better than to command. This was significant in all conditions in which there was not a ceiling effect for command. It was probably true for controls as well, although there was a ceiling deficit.

One important observation is that this finding was as true for cases with good auditory comprehension as well as for those with poor. All patients with poor auditory comprehension (Wernicke's and globals) showed a similar profile of improvement suggesting that there is some basic improvement in control of movement given a reasonably simple stimulus to model whether it is recognized or not. For many Wernicke's aphasics, in fact, much of the apparently apraxic performance to command simply went away in imitation. For global aphasics performance remained apraxic. These findings

TABLE 6 METHODS OF SELECTED PRIOR APRAXIC INVESTIGATION

Reference	*Cases*	*Controls*	*Body part(s)*	*Modality*	*Type(s) of movements*	*Scoring*	*Aphasia measure*
Goodglass and Kaplan (1963)	20 aphasics mixed etiologies, globals excluded	19 non-aphasic brain-damaged cases, mixed etiologies	Arm	Verbal command only	Conventional gesture to complex pantomime	0–3 impressionistic scale	Severity
De Renzi *et al.* (1966)	105 aphasics	40 normals	Buccofacial	Command; if necessary, imitation	Conventional gesture to complex pretending	0–2 impressionistic	Token test
De Renzi *et al.* (1980)	60 aphasics, mixed etiologies; sorted by conventional aphasia diagnosis	40 left brain-damaged non-aphasics, 80 right brain-damaged, 100 normals	Limb ipsilateral to lesion	Imitation only	Conventional and meaningless, static and dynamic	0–3 based on number of repetitions (max of 3) to good performance	(1) Conventional aphasia syndromes, (2) specific measures of speech output
Kertesz and Hooper (1982)	230 aphasics, mixed etiologies	32 left brain-damaged non-aphasics; 72 right brain-damaged; 21 normals	1 oculomotor, 1 buccofacial, 1 respiratory, 15 limb	Command; then imitation as needed	Varying levels of representationality	0–3 based on number of repetitions (max. of 3) but each repetition included more imitation with the command	WAB aphasia quotient (severity)
Lehmkuhl *et al* (1983)	88 aphasics, mixed etiologies, sorted by conventional diagnosis	10 right brain-damaged, 10 normals	Buccofacial, arm, leg and bimanual	Command and imitation separately	Mixed representationality	Quantitative tabulation of total number correct and number of each error type	Severity
Poeck *et al.* (1982)	100 aphasics, mixed etiologies, sorted by conventional diagnosis	Same as above	Buccofacial, arm, leg and axial (very strictly defined)	Command and imitation separately	Mixed representationality	Same as above	Severity

seem to support, in part, the rationale behind the studies from Italy that use imitation exclusively (De Renzi *et al.*, 1966, 1980; Basso *et al.*, 1980, 1987*a,b*) as the response to imitation may be a purer measure of praxis. Those studies also ignore the possibility that there are marked differences in how different aphasics 'comprehend' gesture (Gainotti and Lemmo, 1976; Varney, 1978; Duffy and Duffy, 1981; Ferro *et al.*, 1983; Rothi *et al.*, 1985). In addition, movement in response to command may have more natural validity than movement in response to the necessarily artificial situation of imitating others' movements. Whichever modality is chosen, there will be a modality-specific effect on the findings. The findings do not support methodologies that use modalities interchangeably or additively (Heilman *et al.*, 1982; Kertesz and Hooper, 1982) to evoke the best possible response as the 'best' performance can be so different to each.

A previous study from Italy had demonstrated an important effect of the modality of elicitation (De Renzi *et al.*, 1982), so important that one might conclude that modality of presentation should be a critical element in any operational definition of apraxia. Pöeck *et al.* (1982) did not find a quantitative effect of modality although a significant increase in perseverative errors was noted to command. This finding probably would have generated a significant quantitative effect in our scoring methodology, as perseveration was rated the poorest response based on findings in developmental studies (Kaplan, 1968). In those studies (De Renzi *et al.*, 1982; Lehmkuhl *et al.*, 1983) and ours, effects of modality are seen in patients with good comprehension, thus, it is not simply a matter of bypassing impaired comprehension, whether auditory or gestural. It must be an effect of differential access to movement control (a disconnection explanation) or of differential and perhaps hierarchical effects of different contexts (a processing explanation).

Body part

Each body part was analysed independently. The range of body parts that can be involved in ideomotor apraxia has often not been specified. Liepmann (1908) did not originally consider apraxia of facial or oral movements to be ideomotor apraxia; rather, he classified this as a form of motor apraxia, an impairment of the organization of efferent motor control. Subsequent studies of ideomotor apraxia have taken highly variable approaches to this question. De Renzi *et al.* (1966) did not express a specific position although the structure of the investigated movements suggests that the disorder was viewed as ideomotor apraxia. Most reports have implicitly (Geschwind, 1975) or explicitly (Kertesz and Hooper, 1982; Lehmkuhl *et al.*, 1983) constructed models of ideomotor apraxia that include facial-oral movements. The recent literature does not suggest that buccofacial and respiratory apraxia (at least as tested in the type of tasks in this study) is due to a primarily motor production disturbance.

This form of apraxia was investigated in a manner parallel to limb ideomotor apraxia. Buccofacial and respiratory movements had such similar functional profiles that they may be organized in the same neural systems despite our original clinical bias that some non-fluent cases have much greater difficulty with movements that incorporate a respiratory component. All anterior/central and global cases had significant impairments in buccofacial and respiratory praxis to both modalities.

This finding for buccofacial and respiratory apraxia has been previously reported and is one of the most robust conclusions about ideomotor apraxia (De Renzi *et al.*, 1966;

Kertesz and Hooper, 1982; Lehmkuhl *et al.*, 1983). In our study, in fact, the impairments were correlated with the overall aphasia severity in these non-fluent groups. It is possible that there is extensive overlap of the functional systems required for buccofacial and respiratory movements and for fluent speech. There is little correlation between articulation and buccofacial and respiratory apraxia (De Renzi *et al.*, 1966). It is possible that the neural systems for articulation, being a discrete efferent motor operation, are much less redundantly represented (Schiff *et al.*, 1983). There may be a more restricted motor apraxia of oral movements reflected in speech impairments that is closer to Liepmann's original suggestion (1908). This possible oral motor apraxia may, in fact, be largely congruent with a neural system for articulation, but only objective measures of speech will resolve this question (Ziegler and Cramon, 1985). The theoretical relationship of ideomotor apraxia to the so-called motor apraxias (as well as the conceptually more complex ideational apraxias) is too multifaceted for consideration here.

The situation with limb movements is more complex. Prior investigations have varied between systematic use of the left hand to neutralize effects of hemiparesis and use of the preferred hand when possible. In the present study, possible effects of hand were explored in a particularly important subset of cases, the anterior/central cases who happened not to be hemiparetic. We could find no difference between performance of the hands to either modality or at any level of representation. Within this population the selection of hand does not seem critical. The deficit in movement must occur proximal to activation of the effector motor systems. This finding does not contradict the robust observation that lesions within the mid-callosum can produce ideomotor apraxia restricted to the left hand (Geschwind, 1975; Watson and Heilman, 1983) (a very specific disconnection hypothesis). It also does not distinguish between disconnection or processing hypotheses within the left hemisphere.

For limb ideomotor apraxia the only significant correlation with language measures was between auditory comprehension and movements to command, and this was only observed in patients with poor comprehension. Some earlier reports have also described no or weak relationships between limb ideomotor apraxia and aphasia measures (Goodglass and Kaplan, 1963; Lehmkuhl *et al.*, 1983). Reports from Italy, however, have consistently showed a significant correlation between ideomotor apraxia and aphasia severity (De Renzi *et al.*, 1966, 1980; Basso *et al.*, 1980, 1987*a,b*) but the correlation is only to the token test (De Renzi and Vignolo, 1962). That test is a complex measure, very sensitive to aphasia, but also perhaps to apraxia as it consists of a series of upper limb movement commands. Other studies, including this one, have used language measures not dependent upon following commands with the limbs. Thus, there may be no important functional overlap between the neural systems for language and for limb ideomotor apraxia other than those necessary for access between them. There must be some anatomical overlap, however, given their frequent co-occurrence (discussed below).

Kertesz and Hooper (1982) found significant correlations between language measures and praxis. In fact, they found significant correlations between everything studied (overall aphasia severity, auditory comprehension, repetition, naming, writing and 2 visuospatial measures) with all levels of apraxia. These correlations held for the three aphasic, apraxic groups with good comprehension. It also held for groups who were only tested by imitation. These observations (pervasive correlations between all measures, but correlations that do not distinguish between groups) may also only speak to the inevitable anatomical overlap or interdigitation of the various functional systems for a large set of complex operations. The larger the number of patients, especially ones with large lesions, the more inevitable the finding of wide but undiscriminating correlations.

The situation of axial movements is also complex. Our study found that axial movements were better performed than all other body parts in all aphasic groups, even those with good comprehension. The only prior investigation of this issue apparently found no preferential sparing of axial movements (Pöeck *et al.*, 1982). Again, diverse methods obscure compatible results. First, Pöeck *et al.* (1982) exercised a much more defensible definition of axial than had been originally proposed by Geschwind (1975). They asserted that movements around the midline should define axial. As a consequence they focused on stepping, on symmetrical shoulder movements and on head and eye movements highly dependent upon single directional terms, such as 'Look down'. These are far different types of movements than those explored in this study which focused upon naturalistic movements that recruited the whole body, including the torso, such as, 'Pretend to dance'. It is possible that the different types of movements will simply give different results even if they are both labelled axial.

Several years later, the data in their original report (Pöeck *et al.*, 1982) were reanalysed by Howes (1988). He asserted that, using less conservative statistical methods, the data did demonstrate a preferential sparing of axial movements as defined by the original authors. The authors of the report, in reply (Pöeck and Willmes, 1988), acknowledged that axial movements (their definition) might be spared, depending upon whether the question was framed within aphasic groups or across aphasic groups and that they had not examined the type of movements originally identified by Geschwind.

Representationality

In the present study a significant effect of representationality was observed with less representational acts being consistently better performed than more representational ones for all body parts. No significant interactions with modality or body part emerged suggesting that the effect is a pervasive one of representationality. Prior reports have generally not found this effect (De Renzi *et al.*, 1980; Kertesz and Hooper, 1982; Lehmkuhl *et al.*, 1983), but, again, the discrepancy may be generated in the different methods. In one report (Kertesz and Hooper, 1982), only two of the 15 movements tested would have qualified as non-representational by our study's criteria and several of the representational movements were, in fact, complex pantomimes. Unlike simple gesture, complex pantomime has been consistently demonstrated to be preferentially impaired in aphasia (Cicone *et al.*, 1979; Duffy and Duffy, 1981; Duffy *et al.*, 1984). The other reports have used *very* non-representational movements, such as entirely novel and unnatural hand postures or sequential positions. In one such study (De Renzi *et al.*, 1980), 20% of right brain injured controls are apraxic(!), a finding not replicated by any other method, suggesting that the tasks may not be entirely appropriate to identify ideomotor apraxia.

Other studies have specifically examined the role of representationality on overall performance and in error types. Results have been quite divergent. Kimura *et al.* (Kimura, 1982; Watson and Kimura, 1989) have generally rejected any importance for representationality and have instead focused on the role of the left hemisphere in learning and producing sequential movements. This group has simply considered apraxia for representational movements to be the worst possible case of damaged motor learning. While a basic capacity to learn motor sequences might underlie the development of articulatory and practic functions, there is scant evidence that either has obligatory relationship to the development of language. There is an abundant case literature showing total dissociations between the developed functions of language, praxis and articulation (Heilman *et al.*, 1973, 1974; Alexander *et al.*, 1989, 1990). Two additional studies (Haaland and Flaherty, 1984; Duffy and Duffy, 1989) cannot be compared with the literature reviewed above for several reasons: time post-onset was totally uncontrolled, cases were selected to eliminate impaired patients, and qualitative error measures were so stringent that most performances other studies considered within normal limits were called errors. In our study, the actual movements required for representational and non-representational actions were matched; non-representational was always better. It is possible, however, that non-representational tasks were simply easier. Normals and right brain injured controls are uninformative because they showed a ceiling effect. It is also possible that the commands are more complex (representational movements use 'pretend to'), but the effect was seen in aphasics with good comprehension and even to imitation, so language difficulty explanations may not be sufficient.

Lesion correlations

The classical teaching about the anatomy of ideomotor apraxia was summarized by Geschwind in 1975. In that scheme, the modality of eliciting movement was processed in the appropriate posterior brain region, in particular Wernicke's area for verbal commands. The posterior region then activated motor association cortex for the required body part through white matter connections (typically represented as the arcuate fasciculus) running from temporoparietal regions to the midfrontal regions. The left hemisphere is dominant for these functions, and thus, left frontal lesions produce buccofacial apraxia, right hemiparesis and left limb apraxia. Left parietal lesions produce buccofacial apraxia and bilateral limb apraxia. Axial movements are relatively spared because they do not depend on this system at all but have an entirely different system of efferent pathways. The results of the present study and of the several relevant studies in the literature of the past decade partly support this formulation of Geschwind, at least for limb ideomotor apraxia. Unfortunately, the studies that have examined possible clinico-anatomical correlations for ideomotor apraxia do not lend themselves to simple reconciliation any better than the behavioural studies. Methodologies for labelling patients as apraxic or not differ sharply, and the methods of CT analysis have virtually no common ground. Analysis of this literature and of the place of the current findings in that literature is so constrained by these differences that we have summarized the different methods (Basso *et al.*, 1980, 1987*b*; Tognola and Vignolo, 1980; Heilman *et al.*, 1982; Kertesz and Ferro, 1984) in Table 7.

In the present study buccofacial and respiratory ideomotor apraxia had a high correlation with lesions simultaneously in the frontal operculum and the anterior paraventricular white matter. This is essentially the same finding reported by Tognola and Vignolo (1980). Even the exceptions to this finding in our study were similar to the exceptions in that study, that is, cases having lesions *restricted* to the anterior paraventricular, anterior capsular-striatal region (and perhaps the anterior insula). The parallel between the

TABLE 7 SUMMARY OF STUDIES OF ANATOMICAL-PRAXIS CORRELATIONS

References	*Cases*	*TPO*	*Body part*	*Modality*	*Scoring*	*CT Evaluation*
Basso *et al.* (1980)	123 left brain damaged	Acute 15–90 d; chronic > 290 d	Left arm	Imitation	0–2, based on impressionistic, absolute cut-off based on normals	Total lesion volume: suprasylvian or infrasylvian brain divided into 60 antero-posterior columns, presence of lesion in each
Tognola and Vignolo (1980)	44 left brain damaged; all stroke	21–60 d	Buccofacial	Imitation	Same as above	Visual inspection
Heilman *et al* (1982)	20 left brain damaged, presumably all strokes	Not provided	Arm, side not specified	Command	Correct or not; no criteria provided	Visual inspection
Kertesz and Ferro (1984)	177 left brain damaged, all stroke	Acute. < 30 d, chronic > 90 d	All	Command mixed with imitation	0–3, based on number of repetitions (max of 3), absolute cut-off based on normals	(1) Total lesion volumes; (2) regional check list; (3) impressionist measure of atrophy; (4) posterior asymmetries
Basso *et al* (1987)	129 left brain damaged, all strokes	Acute: 15–30 d	Limb	Imitation	0–3 as with Basso *et al.* (1980)	(1) Large vs small, (2) cortical vs subcortical

neuropsychological findings and the neuroanatomical findings is clear. The overlap of functional systems for buccofacial and respiratory praxis and for fluent language production is paralleled by the overlap in the neural systems. Damage to an extensive opercular-rolandic region and the white matter deep to it or even just extensive damage to the anterior capsular-putaminal-paraventricular region is likely to produce non-fluent aphasia (at least initially) (Alexander *et al.*, 1990) and buccofacial and respiratory ideomotor apraxia. The neural system damaged in the production of articulatory impairment is much smaller, and often contained within the buccofacial and respiratory ideomotor apraxia lesion, in keeping with a discrete efferent motor system (Schiff *et al.*, 1983).

In the present study there was no specific lesion site correlated with limb apraxia. The three prior studies of this question, albeit using much different measures of ideomotor apraxia also found no specific anatomical lesion (Basso *et al.*, 1980, 1987*a*; Kertesz and Ferro, 1984). All three studies reported strong association of apraxia with large cortico-subcortical lesions in the suprasylvian, perirolandic region. In one report, the cases that were apraxic after small lesions had lesions in the parietal lobe (Basso *et al.*, 1980). In another the small, apraxia-producing lesions were restricted to the deep central paraventricular region (Kertesz and Ferro, 1984).

In addition to the 3 group studies of the anatomical correlates of limb ideomotor apraxia, there are case studies describing bilateral limb ideomotor apraxia after parietal lesions (Benson *et al.*, 1973; Damasio and Damasio, 1980; Poncet *et al.*, 1987). One recent case study demonstrated lesion restricted to the subcortical white matter of the inferior parietal lobe with a very detailed MRI (Poncet *et al.*, 1987). Retrospective inspection of cases of conduction aphasia from our study, who as a group were not apraxic, revealed that the two cases with mild limb ideomotor apraxia were also the only two cases with visual field impairments. Perhaps only these 2 cases had lesions that went deep enough to interrupt white matter pathways crucial for praxis.

Heilman *et al.* have proposed that lesions in the parietal lobe and the central/rolandic region may both cause limb ideomotor apraxia but by different mechanisms (Heilman *et al.*, 1982). Lesions in the parietal lobe may damage the very representations of learned movements, thus the patients cannot perform or even recognize the proper movements. Large deep lesions anterior to the parietal lobe produce an intrahemispheric disconnection of posterior praxis representations from anterior efferent systems, but, as the representations are not damaged, patients can still recognize correct movements. In a small group of aphasic, apraxic patients, Heilman *et al.* (1982) demonstrated this dichotomy. No other investigation, ours included, has analysed gesture recognition in quite this manner. In a subsequent review Heilman and Rothi (1985) have utilized diagrams to represent this dichotomy and have placed the schematic representations in the inferior parietal region (supramarginal and angular). The only CT actually published in the original study (Heilman *et al.*, 1982), however, demonstrates a lesion in the superior parietal region. (It is also in the right hemisphere of a 'crossed apraxic'.)

There have been reports of limb ideomotor apraxia after purely subcortical lesions (Naeser *et al.*, 1982; Agostoni *et al.*, 1983; Alexander *et al.*, 1987, 1989; Basso *et al.*, 1987*a*). These are all cases of infarcts in the capsular-striatal territories, and many reach to the anterior-central paraventricular white matter. No definitive conclusion about a specific subcortical lesion and apraxia is possible. Lesions have varied in size and precise location. It has been proposed that left limb apraxia and right-sided hemiparesis may only be seen in these subcortical cases if the lesion extends to the paraventricular white matter adjacent and superior to the body of the lateral ventricle (Alexander, 1989). This would account for the failure to demonstrate a correlation of lesions in the striatum with apraxia. It would also be compatible with the results of Kertesz and Ferro (1984) who were not studying specifically subcortical lesions.

At present it is only possible to conclude that damage to a wide area of the left hemisphere can produce limb ideomotor apraxia. Not all lesions may cause ideomotor apraxia through the same mechanism. Large lesions are particularly likely to cause ideomotor apraxia (Basso *et al.*, 1980). Small lesions that cause ideomotor apraxia will usually be in the parietal white matter or in the central paraventricular white matter, whether damaging representations and connections, respectively, as suggested by Heilman *et al.* (1982), or not remains uncertain.

No prior study has attempted to identify a specific lesion site for axial apraxia. Our study had two complementary results that suggest a possible specific lesion site. First, in anterior cases there was the unexpected finding that axial apraxia had a negative correlation with lesion in the lower motor cortex when there were lesions present in motor association cortex and deep paraventricular white matter. This suggests that left frontal motor systems will control axial movements until they are very extensively damaged. Only after very great damage can some additional system then control axial movements. The effect is specific for that one class of movements. The anatomy of any putative secondary system for control of these movements has to be considered unknown. It could involve the right hemisphere or some other left hemisphere pathway. Freund and Hummelsheim (1985) have elegantly described the systems for bilateral control of axial and proximal muscles that descend from each motor association region. Geschwind (1975) had suggested that direct descending pathways from the left temporal lobe to the pons and then to the midline cerebellum could be such an avenue.

Secondly, in posterior cases only those with temporal isthmus lesion had axial apraxia. Perhaps the finding that lesion in temporal isthmus is correlated with axial apraxia in cases with posterior aphasia is also support for Geschwind's contention that descending pathways from temporal lobe are critical for control and axial movements (Geschwind, 1975) if frontal motor systems cannot be used, either because they are damaged (anterior cases) or they cannot be activated from posterior brain regions.

Conclusions

This study confirms and extends many observations about ideomotor apraxia. First, it is inadequate to diagnose or define ideomotor apraxia without explicit specification of the modality of eliciting movement. Secondly, the functional systems and the neural systems of praxis for various parts of the body are sufficiently different that composite measures of praxis probably have no meaning. Thirdly, the interaction of ideomotor apraxia with aphasia is complex. For patients with poor comprehension, circumvention of auditory modality may substantially alter the picture of ideomotor apraxia. For Wernicke's aphasics, in fact, many cases have virtually no ideomotor apraxia once modality is controlled. Fourthly, buccofacial (and respiratory) ideomotor apraxia have considerable functional and neural overlap with non-fluency. This does not mean that one causes the other or that they are 2 manifestations of the same process, but only that in right-handers the 2 functions may share many of the same neural processes. Fifthly, limb ideomotor apraxia has some neural overlap with aphasia but very little functional overlap. The neural networks for limb ideomotor apraxia seem to include both posterior regions (perhaps in large regions of inferior and superior parietal lobules) and a long series of intrahemispheric connections to more anterior effector systems. This topographically diffuse system of organization and connection may account for the high frequency of limb ideomotor apraxia with suprasylvian and deep lesions that also cause aphasia. Sixthly, the neural mechanism that allows for the relative preservation of a class of whole body movements is unknown. It may involve left hemisphere systems in the temporal lobe that can only operate when completely free of inhibition from the usual frontal motor systems. It has not been proven, however, that right hemisphere systems are not involved.

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APPENDIX: PRAXIS TASKS

	Non-representational	*Representation*
Buccofacial	Open your mouth	Yawn as if sleepy
	Stick out your tongue	Whistle
	Puff out your cheeks	Lick food off your lips
	Wrinkle your forehead	Frown as if angry
	Purse your lips	Kiss
Respiratory	Take a deep breath	Suck on a straw
	Breathe in deeply	Blow out a match
	Breathe out fully	Sniff a flower
	Breathe quickly	Pant as if winded
Axial	Stand up	Stand at attention
	Bend over	Bow
	Turn around	Stand like a boxer
	Look behind you	Dance
	Shrug your shoulders	Stand like a baseball batter
Limb		(Intransitive)
	Make a fist	Hitchhike
	Touch your nose	Salute like a soldier
	Raise your arm	Threaten to hit me
	Wiggle your fingers	Wave goodbye
		A cop stops traffic
		Beckon someone over to you
		(Transitive—pretend to . . .)
		Wipe sweat from forehead
		Throw a ball
		Take off a hat
		Play a piano
		Flip a coin
		Hold a pipe as if to smoke it
		(Double transitive—pretend to use a . .)
		Toothbrush
		Hammer
		Comb
		Spoon to stir
		Saw
		Screwdriver

Brain (1992), **115**, 109–122

SIMPLE REACTION TIME TO FOCAL TRANSCRANIAL MAGNETIC STIMULATION

COMPARISON WITH REACTION TIME TO ACOUSTIC, VISUAL AND SOMATOSENSORY STIMULI

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SUMMARY

We studied the effect of different go-signals on the reaction time in nine normal human subjects trained to respond by rapidly flexing one arm. Reaction times to auditory stimuli were shorter than those to visual or somatosensory stimuli, and were inversely correlated with the stimulus intensity. The reaction time was longest to a transcranial (magnetic or electric) stimulus delivered over the contralateral motor cortex that was sufficiently strong to induce a motor evoked potential in the responding biceps. Conversely, reaction time was shortest to either subthreshold transcranial stimulation over the same scalp position or to transcranial stimulation over the ipsilateral motor cortex regardless of intensity.

Suprathreshold transcranial stimulation to the motor cortex seems to transiently inhibit the neurons responsible for initiation of motor programs involving muscles in which motor evoked potentials have been induced, thereby prolonging the reaction time. On the other hand, a subthreshold stimulus either disinhibits or directly activates such neurons leading to a shorter reaction time. Transcallosal connections between the motor cortices may account for the short reaction time to ipsilateral transcranial stimulation.

INTRODUCTION

In simple reaction time studies a single, unequivocal 'go-signal' is repeatedly presented and the subject is required to respond as rapidly as possible each time with the same, completely and unambiguously described movement (Luce, 1986). The reaction time is defined as the interval between go-signal and onset of movement or electromyographic activity (EMG). During this time the physical signal has to be transduced into the neural information code and travel within the nervous system to the centre(s) for detection, processing and interpretation, although conscious recognition may not be needed. Then the information must be relayed to the response centre(s) where the appropriate response is organized and sent to the necessary muscles for its execution. Finally, the mechanical execution of the response must occur.

Factors such as environmental conditions, signal intensity and modality, state of preparedness, motivation and attention of the subject can alter the duration of the reaction time (Luce, 1986). Recently, Day *et al.* (1989) reported that the execution of a voluntary

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movement in a simple reaction time paradigm can be delayed by a single brain stimulus delivered transcranially over the motor cortex shortly before the usual time of response onset. However, in a similar experiment, Hallett *et al.* (1991) found that simple reaction times were faster in trials with magnetic stimulation than in those trials without. Although it initially appeared that magnetic stimulation was shortening the reaction time to the auditory go-signal, subsequent experiments suggested that the subjects were reacting to the magnetic stimulus itself and disregarding the earlier delivered signal. If so, the simple reaction time to the magnetic stimulus would be shorter by approximately 30 ms than that to an auditory signal.

Shortening reaction time has been described previously when a second signal to which the subject is not supposed to react occurs simultaneously with or shortly after (up to 85 ms) the reaction signal (Nickerson, 1973). This 'intersensory facilitation' is particularly prominent when the two signals are of a different modality (for example, a visual reaction signal and a second, irrelevant auditory signal) and when the interval between the two signals is short (less than 20 ms) (Bernstein *et al.*, 1969). In such cases, shortening the reaction time by 20–50 ms can occur.

The present study was undertaken to define the reaction time to transcranial stimulation (electric and magnetic) in comparison with stimuli of different sensory modalities. In addition, we wanted to evaluate the possible role of intersensory facilitation in the reaction time to transcranial magnetic stimulation. The latter not only stimulates cerebral structures, but also somatosensory (scalp) and auditory receptors.

METHODS

The study was performed on nine right-handed normal human volunteers (age 26–42 yrs; five males, four females). The subjects were seated comfortably on a chair with the right arm slightly abducted at the shoulder and flexed 90° at the elbow so that the pronated forearm rested on a horizontal platform. An auditory warning signal, used for alerting the subject, was given, followed at a randomly varying interval (1–5 s) by a go-signal. In response to the go-signal, the subject was requested to flex the elbow as rapidly as possible to touch the shoulder with the hand (Fig. 1). Reaction time was measured from the go-signal to the onset of biceps EMG activity. Electromyographic activity was recorded with two gold cup electrodes taped 5 cm apart over the subject's biceps and filled with contact gel. Impedance of the electrodes was kept below 3 kΩ for the recording. The EMG signal was amplified and filtered (30–1000 Hz) by Grass amplifiers, and then digitized with a sampling rate of 5000 Hz per channel and rectified. The device delivering

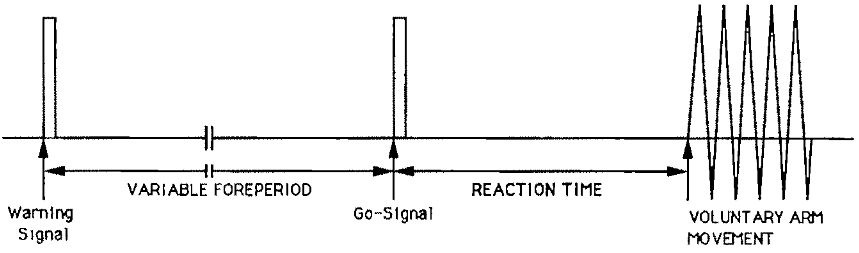

FIG. 1. Experimental design.

the go-signal was triggered with a 100 ms delay after EMG recording began; the total sweep time was −100 ms to 400 ms). All data were collected using an AST personal computer.

In two subjects we recorded the reaction time from the go-signal to both movement onset and EMG onset. Movement onset was recorded using a Grass accelerometer that was taped to the subject's forearm. The signal of the accelerometer was amplified and filtered (30−1000 Hz) by a Grass amplifier, and then digitized (sampling rate 5000 Hz) and rectified.

In each subject several different stimuli were used as go-signals to compare reaction times with different signal modalities (Table). Four auditory signals of different intensity, a visual signal, two somatosensory signals, and transcranial magnetic stimulation of two different intensities delivered over six different scalp positions were employed in all subjects. In addition, transcranial electrical stimulation (TES) and transcranial magnetic stimulation (TMS) while masking hearing with white noise delivered via earphones were used in two subjects. The latter design was employed to isolate, as far as possible, the magnetic stimulus from the loud click produced by the discharging stimulation coil (Counter *et al.*, 1990). The auditory artefact of the magnetic stimulator was greatly attenuated in this manner, but complete masking was not possible despite the use of 100 dB white noise and earplugs.

Magnetic stimulation was delivered with a Cadwell MES 10 magnetic stimulator equipped with an eight-shaped coil in which each component measured 4.5 cm in diameter. When stimulating transcranially the coil was held flat on the scalp with the intersection of the components centred over a defined scalp position. The handle of the coil was held parallel to the sagittal axis of the subject's head, pointing occipitally. During transcranial magnetic stimulation the subjects wore earplugs because of the potential risk of inner ear damage (Counter *et al.*, 1990). Earplugs attenuate the auditory artefact of the stimulator by 30−45 dB but cannot abolish it.

Transcranial stimulation 'over the motor cortex' refers to stimulation over the scalp position that led to the motor evoked potentials of maximal amplitude in the contralateral biceps. This stimulation position was determined with the subject at rest while applying the stimulation (magnetic or electric) at maximal intensity over different scalp areas several times. 'Contralateral motor cortex' refers to the hemisphere contralateral to the arm that the subject was supposed to flex in response to the go-signal, and 'ipsilateral motor cortex' refers to the hemisphere ipsilateral to the responding arm. Subthreshold transcranial stimulation (magnetic or electric) intensity refers to the highest stimulation intensity that in five trials never lead to a motor evoked potential in the contralateral biceps (at 50 mV/Div sensitivity) while the patient was performing the rapid arm flexion. This subthreshold intensity was determined separately for each arm.

Transcranial electrical stimulation was delivered by a Digitimer stimulator model D180 (100 μs time constant) using silver-silver-chloride disc electrodes placed 5 cm apart on the scalp so that unequivocal motor evoked potentials were induced in the contralateral biceps. The stimulus intensity was then kept as high as tolerable to the patient (suprathreshold stimulation), or just below the intensity necessary to evoke the motor potentials at rest (subthreshold). The auditory clicks were generated by a Grass stimulator and delivered by a loudspeaker suspended 15−20 cm over the subject's head. The flash visual signal was generated by a Grass PS22 photic stimulator and delivered at maximal output intensity by a lamp positioned at eye level 30 cm in front of the subject. The somatosensory electric stimulus was generated by a Grass electric stimulator and delivered by two pin electrodes 3 cm apart that were pressed against the subject's left index finger or scalp. The intensity of these electric stimuli was kept at three times sensory threshold determined by the method of limits (Gescheider, 1976).

A total of 30 trials with each go-signal were recorded in each subject. The first 10 trials were considered practice trials and not used to calculate reaction time. During these practice trials the subjects were encouraged to be as rapid and consistent as possible, thus minimizing the variability of the reaction time. Thereafter 20 test trials were recorded and used for the subsequent reaction time analysis. Each recording session was limited to 120 trials (four different go-signals) to avoid fatigue, which would have prolonged the reaction time and introduced an error in the results. In the different subjects the order of the test trials with different go-signals was varied to assure that differences in the reaction time were not due to increased practice or boredom.

For each subject we measured the reaction time in each test trial, and calculated a mean ± standard deviation of the reaction time for each go-signal. Comparison of the results across subjects was performed using one-way analysis of variance (ANOVA) repeated for the different go-signals. Comparison of the reaction times with the different go-signals to each other was performed using one- or two-way ANOVAs collapsing for subjects. Significance level, tested with Scheffé's test, was set at $P < 0.05$.

RESULTS

We found that the reaction time became shorter and much more consistent following the 10 practice trials in all subjects. Figure 2 illustrates this finding for the reaction time measurements for the 90 dB click in one subject.

Comparison of the nine subjects using one-way ANOVAs failed to demonstrate any statistically significant differences across subjects for the reaction times to any of the go-signals. Therefore the results are considered as derived from the total number of *test* trials across subjects. The table summarizes the average mean reaction times for the different go-signals.

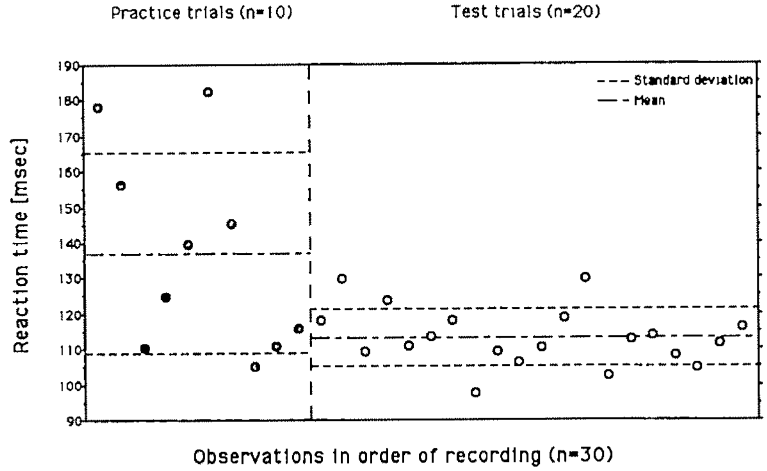

FIG. 2. Example of a subject's reaction times in response to magnetic stimulation with the coil held 2 cm away from the head. (Note the reduction of the mean reaction time and the marked narrowing of the standard deviation when comparing test trials with the practice trials recorded first.)

Comparison of the results obtained using the auditory, visual and somatosensory go-signals demonstrated that the reaction time to the auditory signals was shortest, followed by somatosensory, and then visual (Fig. 3) ($P < 0.001$). Reaction time for the four auditory go-signals was inversely correlated with the intensity of the signal. The shortest reaction times occurred in response to the discharge of the magnetic stimulator which is associated with a click of 140–160 dB (Counter *et al.*, 1990) attenuated to approximately 120 dB by the earplugs.

Reaction time to TMS over the contralateral motor cortex (Figs 4, 5) was markedly different depending upon the intensity of stimulation (100% versus subthreshold, $P < 0.0001$). Reaction time to TMS at 100% intensity was longer than reaction time to auditory, somatosensory or visual go-signals ($P < 0.0001$). On the contrary, reaction time to TMS at subthreshold intensity was significantly shorter than the reaction time to sound of the magnetic stimulator 2 cm away from the head ($P < 0.001$).

Masking did not change the reaction time to TMS over the contralateral motor cortex at either 100% or subthreshold intensity (Fig. 5). Similarly, we found no differences

TABLE REACTION TIMES TO THE DIFFERENT GO-SIGNALS

Go-signal				*Reaction time (ms)* (*mean* ± SD; n = 9 or n = 2*)
Auditory				
Click	60 dB click			126.4±6.1
	90 dB click			121.1±3.7
Discharge magnetic stimulator	Coil 4–6 m behind subject's back			117.8±2.7
	Coil 2 cm over subject's head			111.5±2.0
Visual				
Flash				135.7±2.1
Somatosensory				
Electric stimulation	Left index			131.7±1.8
	Scalp			129.1±2.5
Transcranial				
Magnetic stimulation	100% intensity	Contralateral motor cortex	With auditory masking	155.2±3.0*
			Without auditory masking	154.8±4.7
		Ipsilateral motor cortex	With auditory masking	91.4±3.9*
			Without auditory masking	90.9±4.5
		F3		110.4±3.7
		F4		112.5±4.1
		P3		110.2±4.6
		P4		110.7±3.0
	Subthreshold	Contralateral motor cortex	With auditory masking	87.8±4.1*
			Without auditory masking	87.7±3.7
		Ipsilateral motor cortex	With auditory masking	88.3±4.0*
			Without auditory masking	88.8±4.3
		F3		118.2±4.4
		F4		115.4±4.7
		P3		115.6±3.7
		P4		114.2±3.8
Electric stimulation	Suprathreshold	Contralateral motor cortex		155.4±3.9*
		Ipsilateral motor cortex		91.6±4.7*
	Subthreshold	Contralateral motor cortex		88.9±3.0*
		Ipsilateral motor cortex		89.2±4.1*

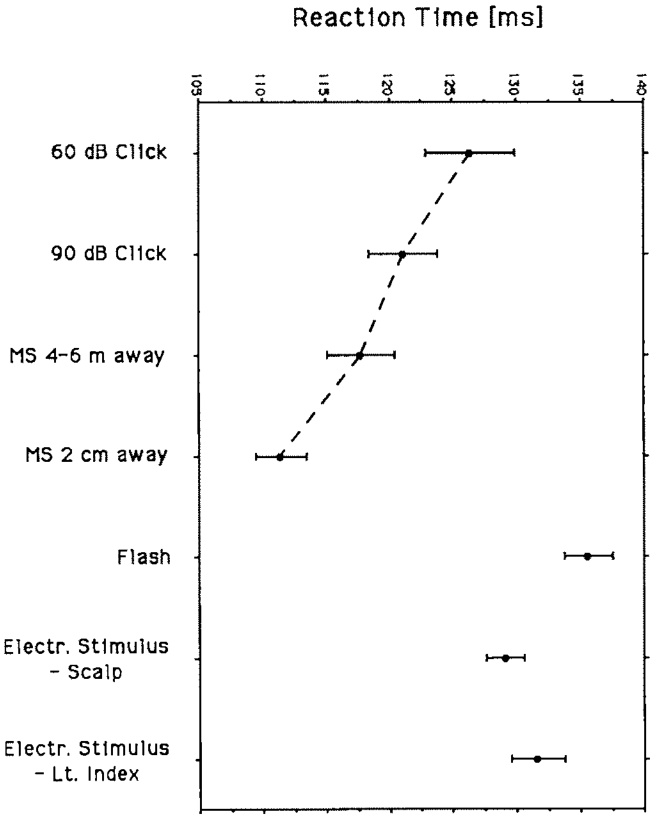

FIG. 3. Reaction times to four auditory, visual and two somatosensory go-signals expressed as mean ± standard deviation The dashed line illustrates the inverse correlation between reaction time and intensity of stimulation.

in the reaction times to TES or TMS over the contralateral motor cortex at sub- or suprathreshold intensities (Figs 5, 6).

Reaction time to TMS at 100% or subthreshold intensity delivered over F3, F4, P3 or P4 did not differ from the reaction time to the magnetic stimulus delivered with the coil away from the subject's head (Fig. 7). However, reaction times to TMS at 100% intensity tended to be shorter than those at subthreshold intensity (Fig. 7). This could be due to the louder auditory artefact associated with the higher stimulation intensity.

Regardless of the intensity of stimulation, reaction time to TMS over the ipsilateral motor cortex was significantly shorter than reaction time to TMS over any other scalp position away from the motor cortex ($P < 0.0001$). There were no significant differences between reaction times to TMS at 100% intensity over the ipsilateral motor cortex, TMS at subthreshold intensity over the same scalp position and TMS at subthreshold intensity over the contralateral motor cortex (Fig. 7). However, reaction time to TMS at 100% intensity over the ipsilateral motor cortex was significantly different from the reaction time to TMS at the same intensity over the contralateral motor cortex ($P < 0.0001$).

The reaction times measured from the go-signals to movement onset as recorded with

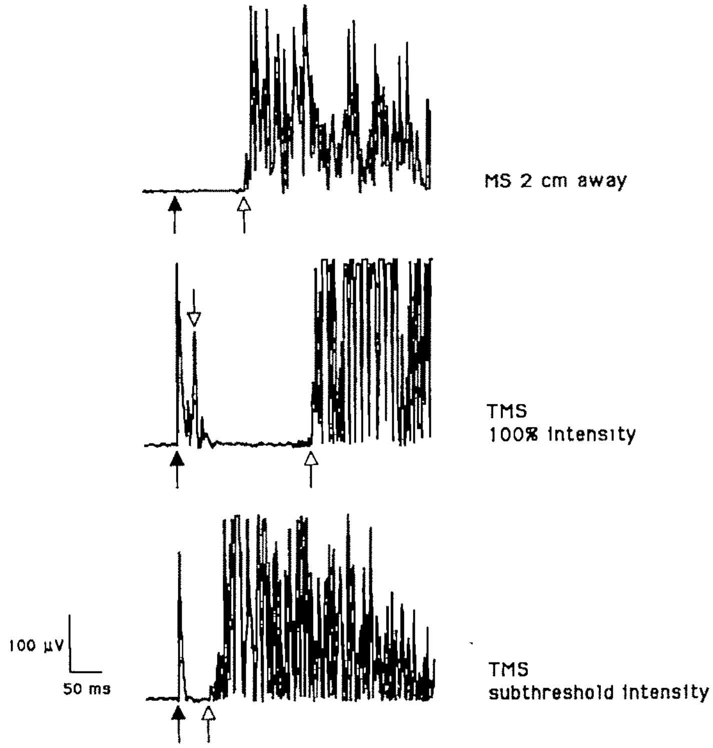

FIG. 4. Example of the recorded EMG activity during reaction to magnetic stimulation with the coil held 2 cm away from the subject's head (*top*), and transcranial magnetic stimulation over the contralateral motor cortex at 100% intensity (*middle*) and subthreshold intensity (*bottom*) The arrows mark the time of the go-signal (black), the onset of EMG activity (white), and the evoked motor potential (stippled). (Note the difference in reaction time to the different go-signals.)

the accelerometer correlated well with those measured to the onset of biceps EMG activity (Figs 8, 9). EMG onset averaged 30–40 ms prior to movement regardless of the go-signal's stimulus modality.

DISCUSSION

This study provides an unique comparison of simple reaction times to go-signals of different modalities using the same subjects, task and testing environment. The differences obtained for the reaction times to auditory, somatosensory and visual stimuli agree with previous studies (Luce, 1986). Our results for the four different auditory signals demonstrate the shortening of reaction times with increasing intensity of the go-signal. Similarly, the difference between reaction times during the first 10 trials and the subsequent test trials (Fig. 2) illustrates the effect of practice on simple reaction time, which has also been previously noted.

The main finding of this study, however, relates to the effects of transcranial stimuli on reaction time. Reaction time to transcranial stimuli delivered over the motor cortex at above motor threshold intensity was significantly longer than reaction time to any

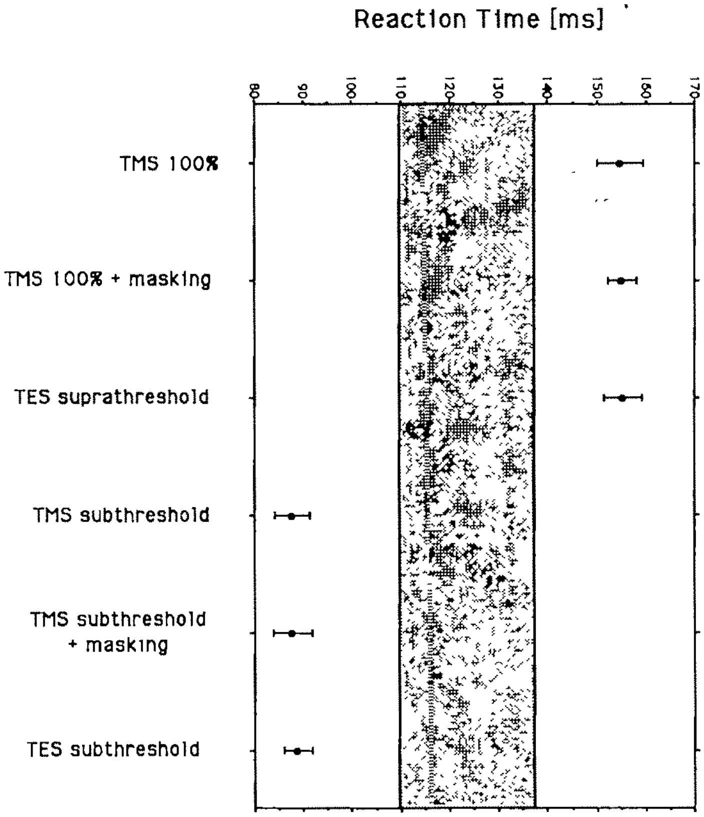

FIG. 5. Reaction time to different types of transcranial stimulation over the contralateral motor cortex expressed as mean ± standard deviation. The results for TMS with auditory masking were obtained from only two subjects (40 trials/condition) The results for TES are derived from only one subject (20 trials/condition). The stippled area marks the range of responses to four auditory, visual and two somatosensory go-signals (*see* Fig. 3).

other go-signal tested. These effects were not present when the transcranial stimulus was delivered over the frontal or parietal areas, which suggests a topographic specificity. These results seem related to the delay of the simple reaction time to an auditory go-signal by a transcranial stimulus delivered over the motor cortex in close proximity to the expected time of onset of the voluntary movement (Day *et al.*, 1989). This effect is also restricted to suprathreshold stimuli that evoke contralateral motor action potentials and depends on the interval between go-signal and transcranial stimulus. When go-signal and transcranial stimulus are given simultaneously, a delay of the contralateral responses but a shortening of the ipsilateral responses may occur (Day *et al.*, 1989).

Focal suprathreshold stimuli to the motor cortex are associated with long reaction times and can prolong the reaction time to an auditory go-signal. We agree with Day *et al.* (1989) that such a transcranial stimulus may transiently inhibit the group of neurons responsible for initiation of a motor program involving the muscles in which motor evoked potentials have been induced. However, we suggest, that at the same time such a stimulus disinhibits or directly activates the neurons responsible for initiation of motor

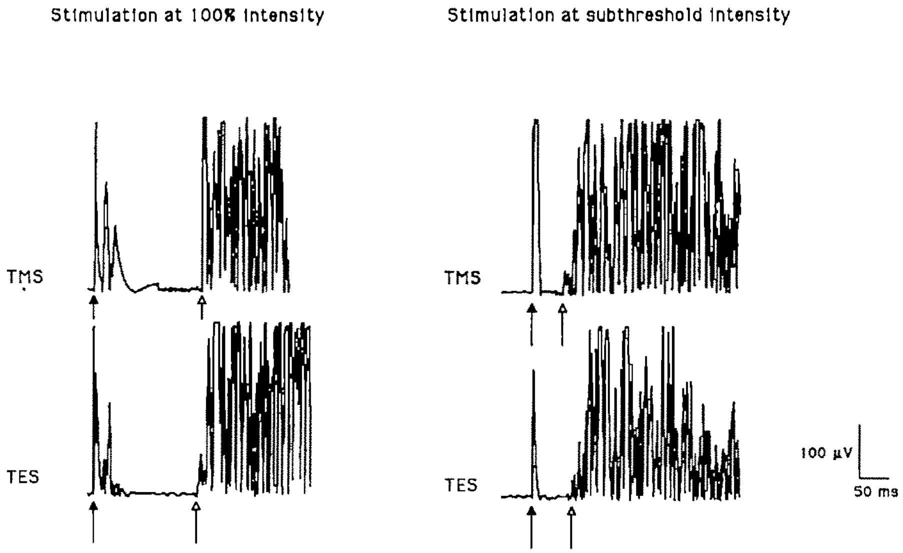

FIG. 6 Example of the comparison between reaction times to TMS and TES over the contralateral motor cortex. The arrows mark the time of the go-signal (black) and the onset of EMG activity (white). [Note the motor evoked potentials in the trials at 100% intensity (*left*). Note the marked difference in reaction time between stimulation at 100% (*left*) and at subthreshold intensity (*right*), and the good correlation between TMS and TES]

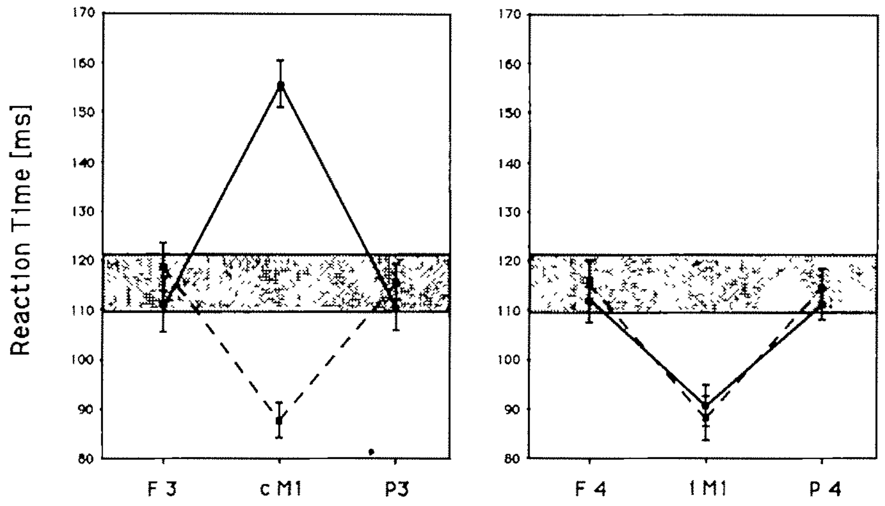

FIG 7 Reaction time (mean ± standard deviation) to TMS at 100% intensity (solid line) and at subthreshold intensity (dashed line) delivered with the stimulation coil centred over different scalp positions The stippled areas mark the range of reaction times to magnetic stimulation with the coil away from the subject's head [Note the marked shortening of the reaction times to TMS at 100% over the ipsilateral motor cortex (i M1) and at subthreshold intensity over the ipsi- and the contralateral motor cortices (i M1 and c M1). Note the marked prolongation of the reaction time to TMS at 100% over the contralateral motor cortex (c M1) Finally, note the tendency of the reaction times to stimulation outside the motor cortex to be shorter for TMS at 100%]

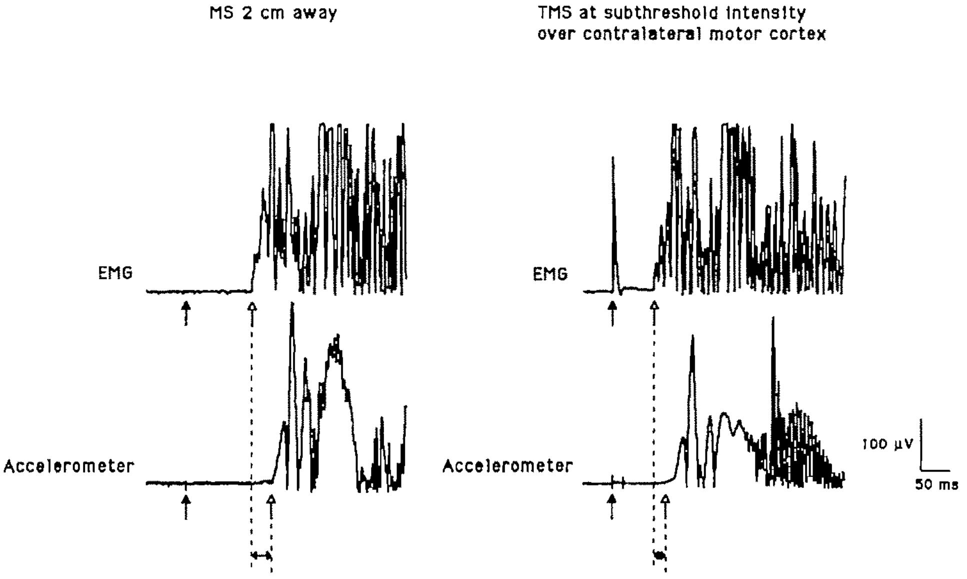

FIG 8. Example of the responses recorded by EMG and accelerometer. Black arrows mark the time of the go-signal, white arrows mark the onset of EMG activity (*top*) of movement (*bottom*). (Note the good correlation of the reaction times measured by these two different methods.)

programs involving other muscle groups (ipsilateral or contralateral). This would explain the short reaction times to suprathreshold transcranial stimuli delivered over the motor cortex ipsilateral to the responding arm. A similar disinhibition or direct activation of a specific neuronal population could account for the short reaction times found to subthreshold transcranial stimuli over the motor cortex.

Subthreshold transcranial stimuli over the motor cortex ipsi- or contralateral to the responding arm may not only be associated with short reaction times but also shorten the reaction times to a go-signal of other modalities. Weak direct currents applied transcranially can shorten the response time to go-signals of different modalities by up to 50 ms depending on the current polarity (Elbert *et al.*, 1981). Jaeger *et al.* (1987) used electric stimuli applied randomly to the right or left index fingers as go-signals, and asked human subjects to respond by moving a lever with the thumb of the stimulated hand. When transcranial weak DC-currents were applied over the sensorimotor cortex, the reaction time shortened by approximately 20–30 ms for ispi- and contralateral responses.

Transcranial stimuli (electric or magnetic), in addition to stimulating cerebral structures, produce an audible click, contraction of the scalp musculature and stimulation of the scalp somatosensory receptors. It is unclear what the subjects are responding to when transcranial stimuli are used as go-signals. Subjects could be responding to the auditory signal, and the short reaction time could be due to intersensory facilitation (Nickerson, 1973) by the concomitant somatosensory scalp stimulation. This seems unlikely, since when the click was masked by white noise, the reaction time to TMS remained unchanged. In addition, intersensory facilitation could not explain the limitation

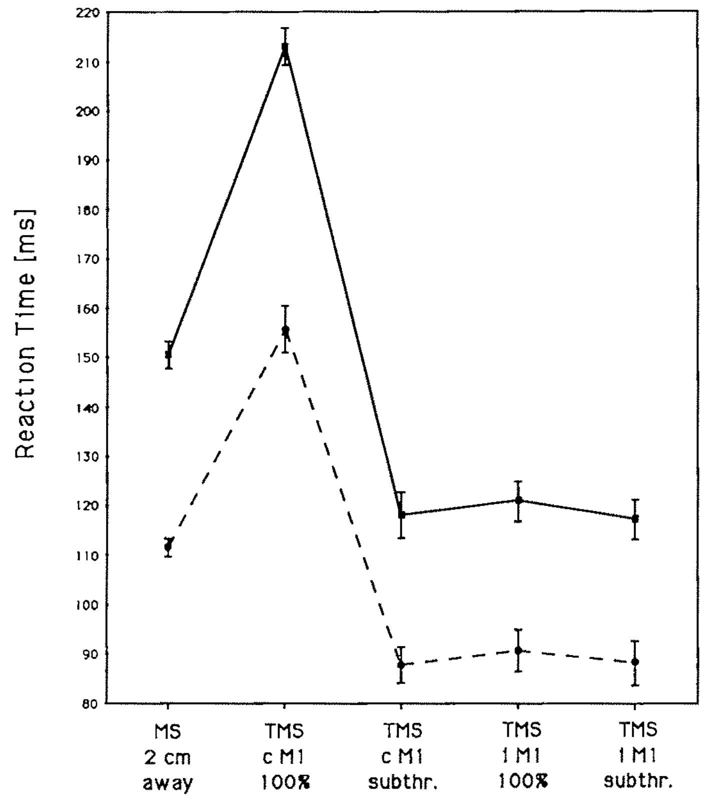

FIG 9 Reaction time (mean ± standard deviation) to different go-signals as measured to onset of EMG activity (dashed line) or of movement (plain line). (Note the good correlation between both methods of reaction time determination)

of the effects of TMS on the reaction time to stimulation over the motor cortex. However, we cannot exclude the possibility that our subjects may be responding to the contraction of the scalp musculature or the stimulation of the sensory scalp receptors, and that subthreshold transcranial stimulation over the motor cortex may accelerate the reaction to this somatosensory stimulus. Further studies on the effects of TMS on the reaction time to other stimuli will be presented in a future report.

Transcranial magnetic stimuli delivered over the motor cortex can inhibit the excitability of the contralateral motor cortex as probed by a second transcranial stimulus (Ferbert *et al.*, 1990) and lead to a transient attenuation of the ongoing ipsilateral voluntary muscle activity (ipsilateral silent period) (Wassermann *et al.*, 1990). Inhibition of the contralateral motor cortex begins approximately 10 ms after the transcranial stimulus and lasts for 50–100 ms (Ferbert *et al.*, 1990). The ipsilateral silent periods evoked in upper extremity muscles start 15–20 ms after the transcranial magnetic stimulus and last for approximately 40 ms (Wassermann *et al.*, 1990). So far, the inhibition of contralateral cortical excitability and the ipsilateral silent period have only been described when applying magnetic stimulation at intensities high enough to evoke motor potentials. However, a cortical stimulus at intensities below motor threshold may activate the same transcallosal, sub- or intracortical pathways and exert similar inhibitory effects. Such inhibition could bring a large number of motor neurons into a synchronous, non-refractory state, thus enabling their rapid, simultaneous activation and lead in turn to a fast response time. A similar role for an inhibitory EMG period has been proposed for the premovement silent period (Conrad *et al.*, 1983; Mortimer *et al.*, 1987).

The short reaction times to subthreshold transcranial stimuli could also be related to effects at the spinal level modulated by feedback from the periphery. Activation of the target muscles by TMS, even if minimal, could result in an excitatory feedback that could modulate the effects of corticospinal projections at the segmental level. Subthreshold motor cortex stimulation reduces the reciprocal inhibition of the median H-reflex by radial nerve stimulation, possibly by corticospinal disinhibition of inhibitory spinal interneurons (Rothwell *et al.*, 1984). Reaction time is shortened by up to 50 ms when a stimulus eliciting a reflex (Michie *et al.*, 1976) or a muscle stretch (Day *et al.*, 1983) in the responding muscle occurs in close temporal proximity to the go-signal. Such a reflex may alter tuning at the spinal level and lead to increased excitability of those motor neurons involved in executing the voluntary response, thereby shortening the reaction time (Gurfinkel and Pal'tsev, 1965). Transcranial magnetic stimulation, even when applied at intensities too low to evoke a recordable motor action potential, could disinhibit or excite the appropriate pool of spinal motor neurons, thus leading to a similar effect. However, reaction time seems independent of the time required for motor neuronal depolarization. The long reaction times to suprathreshold transcranial stimuli are not related to refractivity of spinal motor neurons, since H-reflexes can activate muscles in the middle of the delay period (Rothwell *et al.*, 1989). Therefore, the short reaction time to TMS is most likely related to cortical effects.

Stimulus-linked EMG activity can be recorded in reaction time experiments that use very loud auditory go-signals much before the response-correlated potentials (Luschei *et al.*, 1967). Late muscular responses can be recorded following a transcranial cortical stimulus that evoked a motor action potential (Calancie *et al.*, 1987; Holmgren *et al.*, 1990). Therefore, it could be argued that in our reaction time trials to TMS the early onset of EMG activity did not represent the beginning of voluntary contraction but rather responses to the stimulation itself. However, several factors argue against this. First, stimulus-linked EMG activity is very rarely seen in humans (Luschei *et al.*, 1967) and should be constant for TMS over any scalp region or even 2 cm away from the head, since the auditory stimulus remains unchanged. Secondly, late muscular responses are infrequently seen ipsilateral to the stimulus and are inconsistent in their appearance (Holmgren *et al.*, 1990); therefore, they could not explain the results obtained following TMS over the ipsilateral motor cortex, nor the consistency of the results across subjects. Thirdly, late muscular responses appear at three distinct latencies (50–60 ms, around 100 ms and after 150 ms) (Calancie *et al.*, 1987; Holmgren *et al.*, 1990) but the short reaction times to TMS in our subjects were between 80 and 95 ms. Finally, correlation of the reaction times as measured by onset of both EMG activity and movement should exclude the possibility that stimulus-linked EMG activity or late muscular responses account for our results.

The extremely short reaction time to subthreshold TMS over the motor cortex is remarkable even considering the simple reaction time design and the easy response. Most previous simple reaction time studies found that the shortest response times were approximately 100 ms, using high intensity auditory stimuli (Luce, 1986). This is still over 20 ms longer than the mean reaction time to subthreshold TMS. Accepting parallel processing of the different tasks to be accomplished in the time between go-signal and reaction, a minimum time is still required. Direct activation of the motor system by the subthreshold magnetic stimulus could lead to reorganization of these tasks, even to eliminating some usual steps. It is conceivable that the transcranial stimulus could directly activate the neuronal pool responsible for response initiation in the motor cortex, thus leading to a 'reflex-like' response. This might only be possible in cases of simple reaction time where a single go-signal is coupled with a single, overlearned response. Studying the effects of subthreshold TMS on choice reaction time paradigms may help to further clarify these issues.

We conclude that focal transcranial cortical stimulation can affect brain processes associated with initiation and execution of motor responses. These effects depend on stimulus intensity and localization, and seem related to effects of TMS at the cortical level. The topographic specificity of these effects is supported by experiments where subjects following the go-signal are forced to choose between their right and left hand to execute the response. In such forced-choice reaction time paradigms, transcranial stimulation (direct current) over the sensorimotor cortex affects only the reaction time (Jaeger *et al.*, 1987), while stimulation (magnetic) over the frontal area affects hand selection (Ammon and Gandevia, 1990).

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PERIPHERAL AND CENTRAL DELAYS IN THE CORTICAL PROJECTIONS FROM HUMAN TRUNCAL MUSCLES

RAPID CENTRAL TRANSMISSION OF PROPRIOCEPTIVE INPUT FROM THE HAND BUT NOT THE TRUNK

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SUMMARY

In contrast to the cortical connections to and from the muscles of the hand, the transmission of an afferent volley from the intercostal muscles to the cerebral cortex takes ~10 ms longer than it takes a cortical motor volley to reach the muscle. This disparity in afferent and efferent cortical transmission times could be due to a slower peripheral conduction velocity of intercostal muscle afferents or a slower afferent conduction within the central nervous system. The present study derived peripheral and central conduction times for the truncal muscles from the onsets of the mechanically evoked intercostal and abdominal spinal reflexes and the onsets of the cortical sensory potentials. Mean latencies of the ipsilateral intercostal and abdominal reflexes (evoked and recorded in the mid-clavicular line) were 11.9±0.7 (SEM) ms and 13.7±0.9 ms, respectively; calculated peripheral conduction velocities were 69.4±4.1 m/s and 56.2±2.3 m/s (assuming equal velocities for the sensory and motor axons and an intraspinal delay of 1 ms). Central sensory conduction time (spinal cord to cortex) was calculated by subtracting the peripheral conduction times for the intercostal and abdominal afferents (5.5±0.3 ms and 6.4±0.4 ms) from the onsets of the cortical sensory potentials (19.4±0.8 ms and 25.3±12.3 ms); central sensory conduction times (14.2±1.7 ms and 18.6±2.3 ms) were 8–11 ms longer than central *motor* conduction times. These results demonstrate that peripheral conduction velocities of intercostal and abdominal afferents are not slow, and that, when compared with the extremities, there is a relatively long central conduction time for proprioceptive information from the trunk to the cerebral cortex.

INTRODUCTION

It is well established that the fastest afferent volley from an intrinsic muscle of the human hand takes just as long to reach the cerebral cortex as the fastest corticospinal volley takes to reach the muscle: about 20 ms (Gandevia *et al.*, 1984; Rothwell *et al.*, 1987; Thompson *et al.*, 1987; Gandevia and Burke, 1988, 1990; Gandevia and Plassman, 1988; Plassman and Gandevia, 1989). The same is true for the intrinsic muscles of the foot; transmission times to and from the cortex are each about 40 ms (Burke *et al.*, 1981; Gandevia *et al.*, 1982; Thompson *et al.*, 1987; Macefield *et al.*, 1989*a*). However, the *peripheral* conduction velocities of low-threshold muscle afferents from these distal

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muscles are 11 – 18 m/s faster than the corresponding *efferent* conduction velocities (Macefield *et al.*, 1989*b*). This implies that the *central* conduction time of muscle afferents is longer than for descending motor pathways, partly because of the large number of synapses along the sensory pathway compared with the monosynaptic corticospinal pathway.

By contrast, the total transmission time between the intercostal muscles and cortex is appreciably different for the sensory and motor volleys: the fastest muscle afferents from the 5th interspace arrive at the cerebral cortex after about 21 ms (Gandevia and Macefield, 1989), whereas a rapidly conducting corticospinal volley takes only about 11 ms to reach the muscle (Gandevia and Plassman, 1988). In the study of the afferent intercostal projection recordings were made in a hexagonal array around the vertex with both cephalic and non-cephalic reference electrodes (Gandevia and Macefield, 1989). Results from the two studies imply that either the intercostal muscle afferents have a slower peripheral conduction velocity than the motor axons, a situation opposite to that in the limbs, or the transmission of the afferent volley is slowed within the central nervous system to a greater extent than for the hand and foot. The present study aimed to differentiate between these two possibilities by measuring the peripheral and central conduction times of intercostal muscle afferents. Because it is technically difficult to determine the peripheral conduction velocities of these afferents we derived conduction velocity from the latency of the spinal reflex response to percussion of the intercostal muscle. We also derived peripheral conduction velocities for another set of truncal muscles, the lateral abdominal muscles. The results demonstrate that intercostal and abdominal spinal reflex responses occur at sufficiently short latencies to exclude a major peripheral cause of the relatively long afferent transmission times to the cortex. Thus, while primates have developed both secure cortical projections from distal, proximal and truncal muscles, and rapid corticospinal projections to their motor nuclei, it appears that evolution has favoured rapid afferent transmission to the cortex only for the hand and foot.

METHODS

Eleven experiments were performed on one female and six male subjects (22 – 36 yrs), each of whom was free of apparent respiratory or neurological disorder. Six of the subjects were thin, with a body mass index (weight/height^2) of 18.9 – 23.7; the other subject (male, 35 yrs) had an index of 27.8 Subjects provided informed consent to the experimental procedures, which were conducted with the approval of the institutional ethics committee. All experiments were performed with the subject supine on a bed. Skin temperature of the trunk was monitored at two sites and maintained at 34 ± 1°C.

Stimulation procedures

Mechanical stimulation of the lateral intercostal or abdominal muscles was applied by a solenoid motor (Ling Altec) driven by 1 ms square-wave pulses at 3 Hz from a constant voltage source (MS20, Medelec). The pulse displacement of the stimulator probe was 1 – 2 mm. The motor was held in a multi-axial manipulator fixed to a rigid support, allowing the probe to be brought into firm contact with the intercostal or abdominal muscles and held at a constant position and angle throughout the experiment. The stimulator probe consisted of a cylindrical head (diameter 5 mm, length 20 mm) attached perpendicular to the armature of the motor. For the intercostal muscles the probe was positioned over the 5th, 6th or 7th intercostal space, between the mid-clavicular and mid-axillary lines, and with its long axis parallel to the ribs For the abdominal muscles the probe was positioned at the level of the umbilicus, in the same vertical line at which the intercostal muscle was stimulated. In three subjects attempts were made to evoke intercostal

H-reflexes. For these experiments an insulated tungsten micro-electrode was inserted percutaneously into an intercostal muscle anteriorly and advanced towards the intercostal nerve while delivering constant-current pulses (0.1 ms, < 5 mA, 1 Hz) through the micro-electrode (Gandevia and Macefield, 1989). The optimal intramuscular stimulation site was judged by strong but innocuous twitch contractions of the intercostal muscle medial to the electrode, without involvement of the pectoral muscles and without any radiating cutaneous sensations, at the lowest stimulus intensity. In one experiment a second micro-electrode was inserted posteriorly in the same interspace in an attempt to measure the conduction velocity of low-threshold afferents in the intercostal muscle. A tape-measure firmly applied to the chest and abdominal walls was used to determine the conduction distance along the ribs between the electromyograph electrodes and relevant spinous process (T5–7 for the intercostal muscles, T10 for the abdominal muscles); at the costal level the tape was applied to the interspace rather than to the rib.

Recording procedures

Electromyographic activity (EMG) was recorded with bipolar Ag/AgCl surface electrodes (10 mm diameter) over the intercostal or abdominal muscles in the mid-clavicular line, 1–2 cm medial to, and at the same level as, the stimulation probe. Electrodes were also placed at identical sites contralaterally. Electromyographic activity was amplified (2×10^5), filtered (10 Hz–2 kHz) and rectified. Electroencephalographic activity (EEG) was recorded with platinum alloy needle electrodes inserted into the scalp at the vertex and 7 cm lateral to the vertex, an optimal bipolar configuration for detecting the cortical evoked potentials to stimulation of intercostal nerves (Gandevia and Macefield, 1989). Electroencephalographic activity was amplifed (1×10^5), filtered (10 Hz–2 kHz) and stored with rectified EMG on a five-channel digital averaging and analysis system (MS20, Medelec). The sweep duration was 50 ms. Averages generally consisted of duplicate sets, each composed of 128–512 sweeps.

Experimental protocol

Averages were obtained with the intercostal or abdominal muscles either tonically active or completely relaxed. For the intercostal muscles, subjects were instructed to generate tonic inspiratory intercostal EMG by maintaining an increased lung volume with the glottis open. For the abdominal muscles, subjects performed a weak expulsive manoeuvre. Auditory feedback of EMG was provided to assist the subject in maintaining a constant level of activity. Subjects held their breath at functional residual capacity for control sequences in which the intercostal or abdominal muscles were required to be inactive. Averaging sequences were interrupted to allow the resumption of breathing whenever the subject indicated. For each subject, latency and amplitude measurements were made off-line with cursors from the grand average of duplicate or triplicate sets of averaged data. The Mann-Whitney U-test and paired t tests were used for statistical evaluation of the data.

RESULTS

Mechanical stimulation of the lateral intercostal muscles in six subjects, and of the lateral abdominal muscles in five subjects, consistently evoked short-latency stretch reflexes in the relevant muscles and short-latency potentials on the scalp, indicating that the afferent volley had reached the cerebral cortex. It is assumed that stretch-sensitive muscle afferents are activated by the 1 ms percussion pulses. While there may also be a contribution from cutaneous afferents over the chest wall to the cortical sensory potentials this should occur with a similar onset latency (Gandevia and Macefield, 1989).

Spinal and cortical responses to intercostal percussion

Short-latency reflex responses to percussion of the 5th–7th intercostal muscles could be recorded when the muscles were tonically active during a sustained inspiratory effort but not when the muscles were silent, during a breath-hold at functional residual capacity. For the experiment illustrated in Fig. 1, percussion of the 5th intercostal space evoked an ipsilateral reflex response at 13.2 ms, and a contralateral response at 18.1 ms. Mean

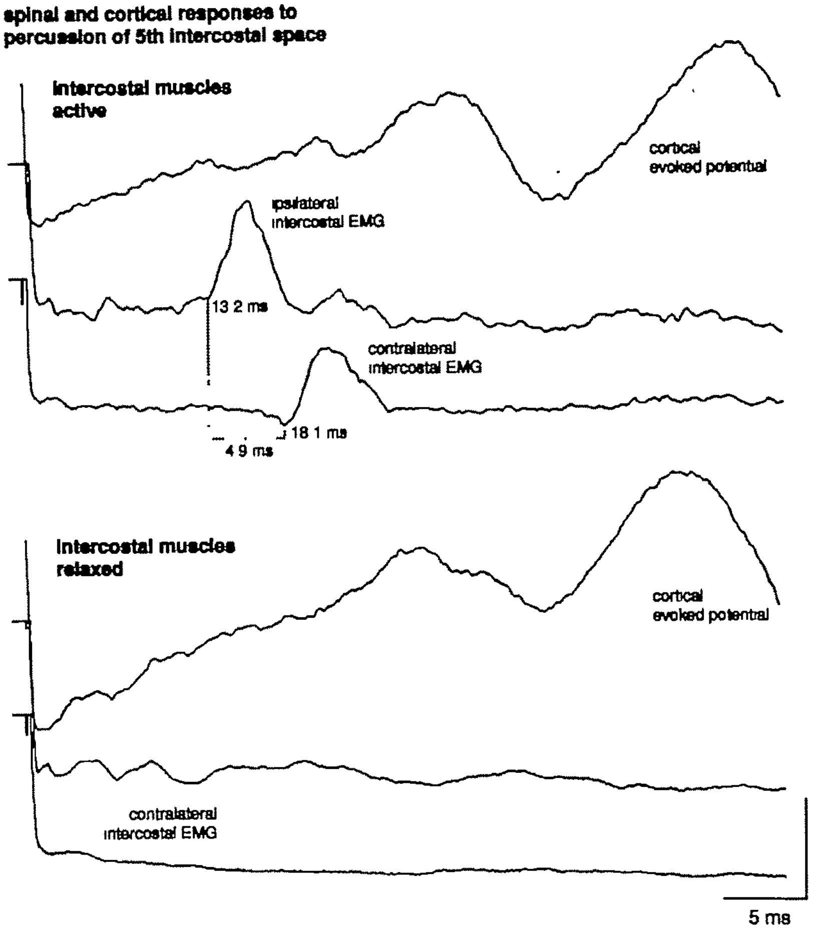

FIG. 1. Response recorded in the 5th intercostal space on the left to percussion in the mid-clavicular line. Upper 3 traces obtained when the intercostal muscles were active in a weak voluntary contraction, and the lower 3 traces when the muscles were relaxed. The top trace in each panel is the evoked cortical response [vertex-C4 (hand area)], middle trace is the ipsilateral EMG response, and the lower trace is the contralateral EMG response. Rectified EMG shown for the intercostal responses Intercostal muscle percussion (1 ms pulse, 3 Hz) evokes a short-latency response in the ipsilateral intercostal muscle when it is active Reflex responses were not detected when the intercostal muscles were relaxed. n = 512. Vertical calibration: EEG, 0.6 μV; EMG, 6 μV

data from all subjects are provided in Table 1. The contralateral reflex was always smaller, often absent (*see* Fig. 2), and occurred on average 3 ms after the ipsilateral response (Table 1). No attempt was made to determine the segmental organization of the reflex by recording from muscles of adjacent intercostal spaces. As indicated in Fig. 1, cortical sensory evoked potentials could be recorded following percussion of relaxed as well as active muscles.

Figure 2 shows the reflex and cortical responses to mechanical stimulation of the 5th intercostal space in a subject in whom short-latency reflexes were recorded ipsilaterally

TABLE 1

	Ipsilateral spinal reflex			*Contralateral spinal reflex*			*Cortical evoked potential*		
	Onset (ms)	*Peak (ms)*	*Amplitude (μV)*	*Onset (ms)*	*Peak (ms)*	*Amplitude (μV)*	*Onset (ms)*	*Peak (ms)*	*Amplitude (μV)*
Intercostal	11.9 ±0.7 (6)	15.4 ±1.0 (6)	7.4 ±1.4 (6)	14.9 ±1.1 (5)	18.3 ±1.3 (5)	2.6 ±0.9 (8*)	19.4 ±0.8 (7)	25.7 ±1.1 (7)	1.08 ±0.38 (7)
Abdominal	13.7 ±0.9 (5)	17.4 ±0.8 (5)	51.2 ±18.4 (5)	19.1 ±3.0 (2)	21.5 ±2.6 (2)	18.3 ±39.5 (5)	25.3 ±2.3 (3)	30.0 ±3.0 (3)	1.11 ±0.48 (3)

*Data from two additional experiments are included in which only contralateral EMG was recorded. Note that contralateral reflex responses were not present in some studies.

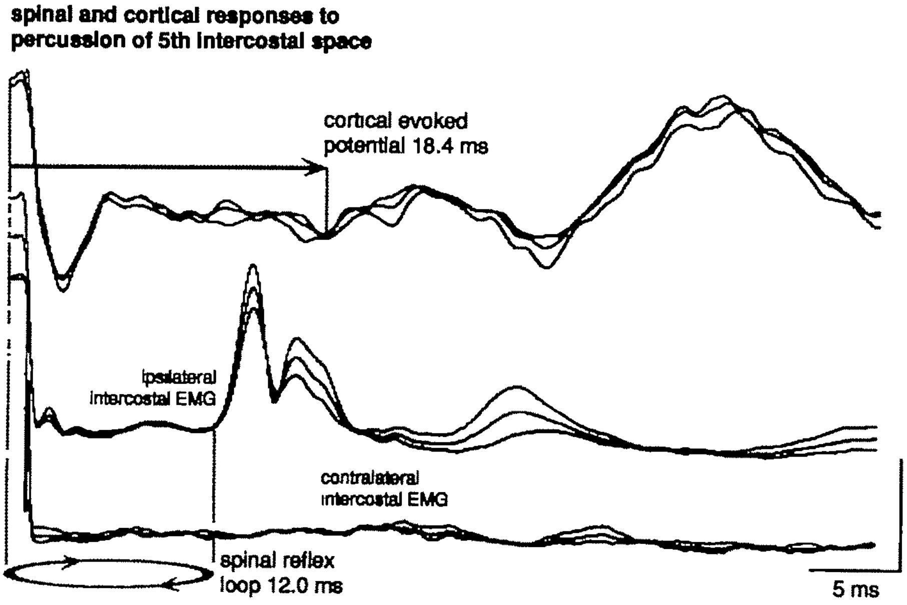

FIG. 2. Spinal and cortical responses to percussion of the 5th intercostal space. Upper traces: cortical evoked potentials; middle traces: ipsilateral intercostal EMG responses; and lower traces: contralateral intercostal EMG responses. Rectified EMG responses have been averaged. Duplicate sets of traces (each 512 sweeps) superimposed with their mean Vertical calibration: EEG, 1 μV; EMG, 10 μV

but not contralaterally. The second peak in the ipsilateral response is an artefact of full-wave rectification, corresponding to the positive phase of the compound muscle action potential (*see* Fig. 3). The peripheral conduction velocities of the intercostal muscle afferents can be estimated by assuming identical afferent and efferent conduction times, and a range of intraspinal and synaptic delays (0.5 – 1.5 ms). The conduction velocities in Table 2 were calculated by doubling the conduction path (between electrodes and spinal cord) and dividing this value by the onset latency of the ipsilateral reflex, after accounting for synaptic transmission. The estimated mean *peripheral* conduction time

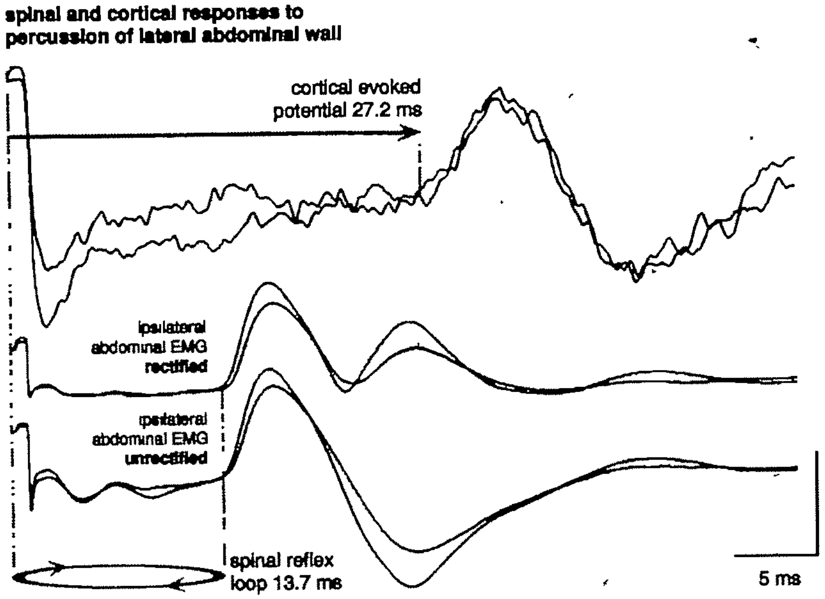

FIG. 3 Spinal and cortical responses to percussion of the anterolateral abdominal wall. Upper traces: cortical evoked potentials, middle traces: ipsilateral abdominal EMG (rectified); and lower traces: ipsilateral abdominal EMG (unrectified). Duplicate sets of traces, each composed of 512 sweeps, are shown superimposed. Vertical calibration: EEG, 0.6 μV; EMG, 100 μV. In this subject responses to abdominal percussion were evident in single trials

TABLE 2

	Ipsilateral spinal reflex		*Estimated conduction velocity (m/s)*		
	Latency (ms)	*Conduction path (cm)*	*Assuming 'central' delay of 0.5 ms*	*1.0 ms*	*1.5 ms*
Intercostal (n = 6)	11.9 ±0.7	37.3 ±1.5	66.2 ±3.7	69.4 ±4.1	72.8 ±4.5
Abdominal (n = 5)	13.7 ±0.9	35.4 ±1.5	54.4 ±1.9	56.2 ±2.3	58.9 ±2.4

for the intercostal motor and sensory axons was 5.5±0.3 (SEM) ms, based on an intraspinal and synaptic delay of 1 ms, and is comparable with the motor conduction time determined by electrical stimulation over the spinal cord (6.1±0.7 ms for the 6th–7th interspaces; Gandevia and Plassman, 1988). Well-defined cortical responses are evident in Fig. 2. The initial cortical component occurred at the same latency as that evoked by electrical stimulation of single intercostal nerves (Gandevia and Macefield, 1989; *see* Table 1), but the morphology of the cortical negativity was usually simpler following mechanical stimulation. Subtracting the peripheral conduction time from the onset latency of the cortical potential gives the *central sensory* conduction time, 14.2±1.7 ms. By contrast, the *central motor* conduction time for the intercostal muscles is only 6.2±1.2 ms (Gandevia and Plassman, 1988).

Spinal and cortical responses to abdominal percussion

Percussion of the lateral abdominal wall, at the level of the umbilicus, evoked short-latency reflex responses in relaxed as well as active muscles. Figure 3 illustrates duplicate records from a subject performing a weak voluntary effort; both rectified and unrectified EMG from the ipsilateral side are shown. In this subject the ipsilateral spinal reflex was very secure (visible in single sweeps), but was absent contralaterally. As indicated in Table 1, the amplitude of the reflex response was greater than that of the intercostal muscles ($P = 0.050$, Mann-Whitney U-test). Cortical latencies were also significantly longer from the abdominal muscles ($P = 0.026$, Mann-Whitney, U-test), but their amplitudes were similar. Estimated peripheral conduction velocities are given in Table 2. For an equivalent intraspinal delay, calculated conduction velocities were significantly lower for the abdominal than the intercostal muscles ($P < 0.05$, paired t tests). The estimated mean *peripheral conduction time* was 6.4 ± 0.4 ms, assuming a 1 ms synaptic delay; the peripheral motor conduction time to the lateral abdominal muscles in the mid-clavicular line is 5.4 ± 0.2 ms (Plassman and Gandevia, 1989). The *central sensory* conduction time, estimated from the peripheral conduction time and the onset of the cortical evoked potential, was 18.6 ± 2.3 ms, 10 ms longer than the *central motor* conduction time (8.5 ± 0.4 ms; Plassman and Gandevia, 1989).

Electrical stimulation of intercostal nerves

In three subjects micro-electrodes were used to apply focal stimuli to the intercostal nerve in an attempt to evoke H-reflexes, the electrical equivalent of myotatic reflexes. As previously noted by Pradhan and Taly (1989), F-waves but not H-reflexes could be obtained. Figure 4A shows superimposed F-waves evoked by delivering supramaximal stimuli to the intercostal nerve. By subtracting the latency of the M-wave from that of the minimal F-wave, and allowing 1 ms for 'turn-around time' at the motor neuron, the conduction velocity of the fastest motor axons can be determined (Kimura *et al.*, 1984; Burke *et al.*, 1989). For the subject represented in Fig. 4A the calculated motor conduction velocity (68.2 m/s) was close to that estimated from the latency of the ipsilateral spinal reflex (67.3 m/s), the latter value assuming equivalent velocities for sensory and motor axons.

In one subject a second micro-electrode was inserted near the 7th intercostal nerve posteriorly, 4 cm lateral to the midline, in an attempt to determine directly the afferent conduction velocity between the anterior stimulating electrode and the posterior recording electrode. Electromyographic interference from nearby back muscles prevented recording of a definite sensory volley, but motor conduction velocity was determined along this intercostal segment by measuring the difference in onset latency of the intercostal EMG when stimulating at the posterior and anterior electrodes. This is illustrated in Fig. 4B; again, the calculated conduction velocity in this subject (62.8 m/s) was close to that estimated from the latency of the ipsilateral spinal reflex (61.2 m/s).

DISCUSSION

The novel findings of the present study are that mechanical stimulation of the intercostal muscles evokes short-latency spinal reflexes, previously described for the abdominal muscles (Kondo *et al.*, 1986; Kondo and Bishop, 1987), and that stimulation of the

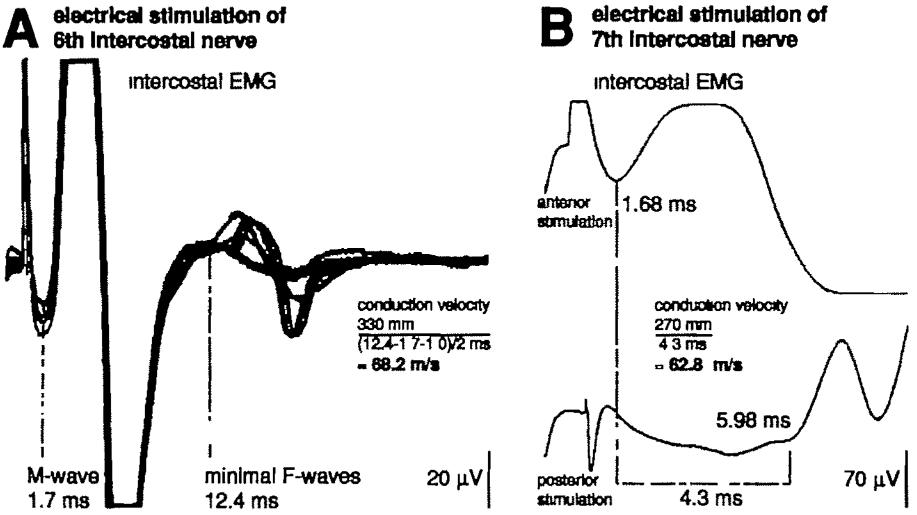

FIG. 4. A, F-wave responses in the 6th intercostal space to supramaximal stimulation of the 6th intercostal nerve. Twenty-five responses superimposed at high gain. Measurement of the minimal F-wave latency allows calculation of the estimated motor conduction velocity. B, responses of the 7th intercostal space to near-nerve stimulation at two sites. n = 16. Estimates of motor conduction velocity based on either method corresponded closely with those obtained using the spinal reflex times (*see* Table 2 and text). Panels A and B depict data from different subjects.

abdominal muscles evokes short-latency cortical sensory potentials, previously reported for the intercostal muscles (Gandevia and Macefield, 1989). Of greater significance, though, is the differentiation between the peripheral and central factors responsible for the long transmission time for proprioceptive inputs from the trunk to the cerebral cortex, and the comparison of this delay to that for afferents from the hand and foot.

Features of the spinal reflexes of truncal muscles

Percussion of the lateral intercostal muscles of the 5th–7th interspaces evoked a single short-latency (~12 ms) reflex contraction in the stimulated muscle and, usually, a contraction of the contralateral muscle about 3 ms later. Because EMG was recorded at identical sites on both sides, this 3 ms difference must be due to oligosynaptic transmission of the afferent volley to the contralateral motor neurons. When present, the contralateral reflex was smaller than the ipsilateral response; vibration of human intercostal muscles evokes a tonic contraction ipsilaterally but not contralaterally (Homma *et al.*, 1978), and the contralateral response to percussion of the erector spinae muscles is smaller than the ipsilateral response (Dimitrijevic *et al.*, 1980). Both the ipsilateral and contralateral intercostal reflexes were dependent on the level of excitation in the (inspiratory) intercostal motor neuron pool: reflexes were present during inspiratory efforts but absent during apnoea. The phasic stretch reflex of the abdominal muscles (Hagbarth and Kugelberg, 1958; Kondo *et al.*, 1986; Kondo and Bishop, 1987) was occasionally expressed contralaterally, but at a smaller amplitude. The abdominal reflex was more potent than the intercostal reflex; its absolute amplitude was greater and it could be elicited in relaxed as well as active muscles. Furthermore, H-reflexes can be evoked in the abdominal muscles (Kondo and Bishop, 1987), but not in the intercostal muscles (Pradhan and Taly, 1989; present results). These differences can be explained by a greater synaptic security between afferents from the abdominal muscles and their α motor neurons. Afferent axons from the intercostal muscles may also have a slightly higher electrical threshold, although the current levels required to evoke cerebral potentials from single intercostal nerves (<3 mA; Gandevia and Macefield, 1989) were comparable with those used in the upper and lower limbs (Gandevia and Burke, 1988, 1990; Macefield *et al.*, 1989*a*,*b*).

An apparent assumption for our calculations of the 'central' component of afferent transmission time is that the latency of both the cortical potential and the reflex response evoked by the tap are due to activation of the same class of afferent fibre. While this assumption can probably be justified, it is not strictly necessary because activation of low-threshold cutaneous or muscle afferents in the intercostal nerves produces cerebral potentials with the same onset latency (Gandevia and Macefield, 1989). Furthermore, the short-latency tendon jerks in abdominal and intercostal muscles are likely to be mediated by muscle spindle rather than cutaneous afferents (Hagbarth and Kugelberg, 1958). An electrically evoked spinal reflex from *high-threshold* afferents of the abdominal skin has been described (Hagbarth and Kugelberg, 1958), but its latency is twice as long and it is unlikely that these afferents would be activated by the relatively weak percussion employed in the present study. Even if, as for the hand and foot, low-threshold cutaneous and muscle afferents from the trunk have identical peripheral conduction velocities (Macefield *et al.*, 1989*b*) this will not affect the conclusion that truncal afferents have a relatively slower central projection than those from the distal extremities. The disparity between sensory and motor central conduction times would be greater (by 5–6 ms, *see* Table 1) if the latency of the *peak* of the primary cortical potential has been used instead of the *onset* of the N20 homologue.

Conduction velocity of truncal muscle afferents

Conduction velocities were estimated from the onset latency of the ipsilateral stretch reflex, which contains four sources of delay: transduction of the mechanical stimulus, propagation of the afferent volley to the spinal cord, intraspinal conduction and monosynaptic or oligosynaptic transmission to the α motor neurons, and efferent conduction to the EMG electrodes. The transduction delay has been ignored in our calculations; the errors in knowing the exact site of stimulation and the exact conduction distance are likely to be greater than the error in omitting transduction times. For example, even if we subtract 3 cm from the afferent limb of the peripheral conduction distance, the calculated conduction velocities would differ by <4%. Besides, the percussive stimulus would tend to spread mechanically, possibly exciting afferents proximal to the immediate site of stimulation. Assuming that afferent and efferent conduction times are equal, the calculated velocities, incorporating intraspinal and synaptic delays of 1 ms, are comparable with the intercostal motor conduction velocities determined either by direct stimulation or by measurement of minimal F-wave latencies. These values are, however, less than those reported by Pradhan and Taly (1989), who used surface stimulation of the 7th–11th intercostal nerves at two sites and measured the latency difference from the onset of abdominal EMG. Their calculated mean conduction velocities ranged from 71.7 ± 1.4 (SEM) m/s to 75.1 ± 1.1 m/s. These values may be inflated because a caliper rather than a tape-measure was used to determine conduction distance, the measured arc may well be longer than the distance along the surface of the rib. Our calculated velocities were lower; conduction distances were determined by a tape-measure applied along the intercostal space, i.e. close to the intercostal nerve. Hagbarth and Kugelberg (1958) calculated an intercostal conduction velocity of 55 m/s.

It is well established that the fastest motor axons conduct slower than the fastest sensory axons in a mixed peripheral nerve (Dawson, 1956; Gilliatt *et al.*, 1961). For example, motor axons to abductor pollicis brevis in the hand and abductor hallucis in the foot conduct at 57.2 ± 0.8 m/s and 43.2 ± 0.9 m/s, respectively (Thomas *et al.*, 1959), whereas low-threshold afferents from these muscles conduct at 74.7 ± 2.5 m/s and 54.7 ± 1.4 m/s (Macefield *et al.*, 1989*b*). Unfortunately, the latter study was based on the proximal limb segment, whereas the efferent conduction study of Thomas *et al.* (1959) dealt with the distal limb segment, in which conduction velocities may be expected to be slightly slower. However, our estimated conduction velocities for afferents and efferents of the intercostal and abdominal muscles (69.4 ± 4.1 m/s and 56.2 ± 2.3 m/s) fall within the range of afferent conduction velocities along the proximal segment of an upper or lower limb (Macefield *et al.*, 1989*b*), with the conduction velocities for intercostal muscle afferents being closer to those from the hand muscles and the conduction velocities for the abdominal muscle afferents being closer to those from the foot.

Peripheral and central delays in the cortical projection of truncal afferents

The disparity in sensory and motor transmission times between the intercostal muscles and cortex has only recently been noted (Gandevia and Macefield, 1989); in measuring the latency of the cortical response to stimulation of the abdominal muscles, and comparing this with recent data on motor conduction time between the cortex and abdominal muscles (Plassman and Gandevia, 1989), the present study has shown that this disparity applies also to the abdominal muscles. Figure 5 illustrates the magnitude of the difference in sensory and motor transmission times between the cortex and several muscles of the upper limb, trunk and foot. Sensory and motor transmission times are identical for intrinsic muscles of the hand and foot, but sensory transmission is some 5 ms longer for muscles of the forearm, upper arm, and shoulder. This disparity doubles for the intercostal muscles and is three times greater for the abdominal muscles. Based on our measurements of peripheral and central conduction times, we conclude that the delayed transmission of muscle afferent volleys from the truncal muscles to the cerebral cortex reflects slowing within the central nervous system; some central slowing of afferent transmission is also apparent to a smaller extent for proximal muscles of the upper limb (Fig. 5). As mentioned above, the afferent volleys from the skin overlying the intercostal muscles arrive at the cerebral cortex with a latency identical to that for afferents from the muscles themselves (Gandevia and Macefield, 1989). In addition, Jörg *et al.* (1982) have measured cortical latencies to electrical stimulation of limb and truncal dermatomes; their values for cutaneous afferents are comparable with our values for muscle afferents (*see also* Gandevia and Burke, 1988, 1990; Gandevia and Macefield, 1989; Macefield *et al.*, 1989*a*). This implies that the source of the central delay may be similar for low-threshold muscle and cutaneous afferents, and may be composed of both slower afferent conduction within the ascending tracts of the spinal cord and more synaptic delays.

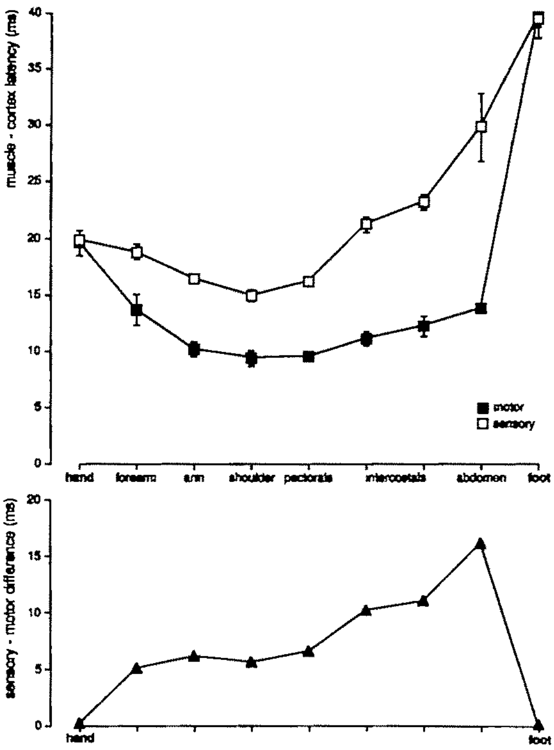

FIG 5. Total conduction time from the cortex to the muscle, and from the muscle to the cortex is plotted for a range of muscles. Muscles include: thenar muscles, extensor digitorum communis, biceps brachii, deltoid, pectoralis major, intercostal muscles at two levels, lateral abdominal muscles and intrinsic muscles of the foot. Data for total afferent conduction time are derived from Gandevia and Burke (1988), Gandevia and Macefield (1989) and Macefield *et al* (1989*a*). Values for abdominal muscles are those derived from the present study. For the intercostal muscles there is no major prolongation of afferent conduction time if cerebral potentials were evoked by electrical or mechanical stimuli. Data for the total motor conduction times are derived from Thompson *et al.* (1987), Gandevia and Rothwell (1987) and Gandevia and Plassman (1988). Mean ± SEM. The lower panel depicts the disparity between the total afferent and total efferent conduction times. This discrepancy is most marked for truncal muscles but is absent for intrinsic muscles of the hand and foot.

Functional implications

Estimated central motor conduction times increase progressively as the distance from motor cortex to spinal motor nuclei increases, consistent with a rapidly conducting corticospinal motor volley of approximately 65 m/s to upper limb, truncal and probably to lower limb motor nuclei (e.g. Gandevia and Plassman, 1988). The estimated central sensory conduction times from muscle (and cutaneous) afferents are as short as the motor conduction times only for afferents from the distal extremities, i.e. the hand and foot. Perhaps primates have evolved a rapidly conducting system for all volitionally generated movements, including those involving the respiratory muscles (*see* Macefield and Gandevia, 1991), but only for the dextrous hand (and foot) has it been advantageous for the cerebral cortex to acquire rapid access to sensory feedback about the movement. Fine manipulative control is particularly dependent upon feedback from the hand (e.g.

Rothwell *et al.*, 1982; Gandevia *et al.*, 1990; Johansson, 1991), but whether control of the truncal musculature is less reliant on peripheral feedback requires investigation. Certainly, the neural substrates are available for both segmental and supraspinal control of the trunk, but the present data would suggest that primate evolution may have been less dependent upon a need for rapid cortical acquisition of information from the trunk than on the need to move the trunk rapidly for manoeuvres such as phonation or for the stabilization required for reaching and subsequent movements of the hand.

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SHORT-TERM SYNCHRONY OF MOTOR UNIT DISCHARGE DURING WEAK ISOMETRIC CONTRACTION IN PARKINSON'S DISEASE

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SUMMARY

Short-term synchrony between the discharges of motor units has been assessed in Parkinson's disease (PD) and normal man. The discharges of single motor units were recorded in the extensor digitorum communis (EDC) muscle of the forearm or the tibialis anterior (TA) muscle of the leg during weak, voluntary isometric contraction. Short-term synchrony was defined as a narrow peak (total width <25 ms) in cross-correlograms constructed from the discharges of pairs of motor units. There was no difference in the incidence of short-term synchrony between PD and normal age-matched subjects for either the EDC or TA muscle. On average, 60% of pairs of motor units exhibited synchrony, but this varied between 0% and 100% for both groups. The amount of short-term synchrony was assessed as the probability (above chance) of discharge of one motor unit with respect to the other. In TA, but not EDC, this index was greater for PD than for normal subjects. The high indices of synchrony in TA in PD were not related to lower discharge rates of motor units. Parkinson's disease subjects, but not normal subjects, also showed broad correlations that were invariably associated with periodic discharges in the range 4–6 Hz. In some instances, a peak of short-term synchrony was observed superimposed on the broad correlation. The periodic correlograms were often associated with overt tremor which accompanied the contraction. Motor units occasionally discharged paired impulses (doublet discharges) with short interspike intervals of 5–15 ms (normal and PD) or, as a more persistent feature in PD, longer interspike doublets (20–60 ms) associated with periodic synchrony (4–6 Hz). The abnormal discharge characteristics of motor units are discussed in relation to the bulbospinal control of presynaptic drive to motor neurons in PD.

INTRODUCTION

It is commonly observed in man that the discharges of motor units within a muscle show a degree of synchronization over a short time span of ±5–10 ms. Such synchronization occurs more frequently and to a greater degree in muscles used for fine control, such as the intrinsic muscles of the hand (Datta and Stephens, 1990). It is also exaggerated in muscles that have undergone training to improve performance in explosive tasks such as weightlifting (Milner-Brown *et al.*, 1975) and it is associated with fatigue (Buchthal and Madsen, 1950; Person and Mishin, 1964). It has been proposed from animal studies that synchronized discharges of a pool of neurons may be caused by simultaneous postsynaptic potentials arising from discharges in common presynaptic stem fibres (Perkel *et al.*, 1967; Sears and Stagg, 1976). The time course of synchronization, as seen in the peak of a cross-correlogram formed from the discharges of two neurons, may be

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estimated from the time course of the unitary postsynaptic potentials created by impulses in the common presynaptic axons, and the change caused in the probability of discharge of each neuron (Kirkwood and Sears, 1978; Fetz and Gustafsson, 1983).

It has been argued (Datta and Stephens, 1990), on the basis of cross-correlation histograms predicted from postsynaptic potential parameters (Kirkwood and Sears, 1978), that the brief form of synchronization between human motor units, as reflected in a peak of about 10 ms duration in the cross-correlogram, is best defined as short-term synchronization originally described by Sears and Stagg (1976). Substantial synchrony spanning a broader period than short-term synchrony has been recognized as arising from synchrony in the presynaptic neurons impinging upon motor neurons (Kirkwood *et al.*, 1982), although the boundary between short-term and broad-peak synchrony is not well defined, at least for human motor neurons (Datta and Stephens, 1990). Nevertheless, the assessment of short-term synchrony in man has provided predictors of the distribution of activity in common presynaptic stem fibres to motor neurons active during different tasks. Synchrony between motor units of synergist muscles is less evident than within a muscle (Deitz *et al.*, 1976; Powers *et al.*, 1989; Bremner *et al.*, 1991*a,b*). This difference reflects the expectation that a smaller proportion of shared inputs exists between heteronymous motor neuron pools.

Several studies have investigated the relation between synchrony of motor unit discharge and physiological tremor (Taylor, 1962; Dietz *et al.*, 1976; Allum *et al.*, 1978). While these studies suggest that the grouping of motor neuron discharges seen during tremor may be caused by a number of mechanisms, it is evident that short-term synchrony arising from shared inputs will inevitably contribute to tremor. Short-term synchrony could therefore limit the precision of a sustained, isometric contraction but would not impair, and indeed might augment, fast, alternating movements.

In studies based largely on observations of synchrony of discharge of γ motor neurons in the cat we have proposed that a bulbospinal system can actively inhibit presynaptic inputs that synchronize efferent output (Davey and Ellaway, 1988; Baker *et al.*, 1991). This bulbospinal pathway descends in the dorsolateral funiculus and involves monoaminergic transmission. A reduction in noradrenalin and indolamine content of the spinal cord has been reported in Parkinson's disease (Scatton *et al.*, 1984) which, if it involved this bulbospinal pathway, would result in an increased tendency for motor neuron discharges to be synchronized. Two previous studies have reported synchrony of motor unit discharge in Parkinson's disease but differ in their stress on short-term (Dietz *et al.*, 1976) and broad synchrony (Dengler *et al.*, 1986), respectively. This study was designed to determine the incidence and degree of short-term synchrony in Parkinson's disease and to compare the situation with normal man. Preliminary accounts of the work have been published (Davey *et al.*, 1986*a,b*).

METHODS

Subjects

Volunteer subjects with Parkinson's disease (PD) were recruited mainly from people attending hospital for consultation. In every case the diagnosis of PD had been made or confirmed by a consultant neurologist. No other specific criteria were used in the selection of PD subjects. However, subjects were precluded from the study if they had incurred any additional neurological disorder. All subjects were receiving treatment with either L-dopa or a dopamine analogue unless indicated otherwise in the text. Recordings were not made within an hour of a subject taking anti-parkinsonian or other drugs. Age-matched normal control subjects with no known neurological disorders were recruited mainly from our colleagues, families and friends. Both groups of subjects were interviewed before participation so that we could exclude those who had overt motor problems other than those associated with PD.

Ethical approval for this study was obtained from the relevant Schools of the University of London and the hospitals attended by the patients. The procedures were explained to all subjects and they signed a consent form before participating in the study.

Electrophysiological recording

The discharges of single or multiple motor units were recorded with two concentric needle electrodes inserted into the same muscle with a separation of 1.5 to 3 cm. The electrodes were connected to a pre-amplifier having a lower bandwidth limit of 300 Hz, to avoid slow baseline fluctuations, and an upper limit of 3 or 5 kHz, to minimize distortion of single motor unit discharges. A combined voltage threshold and time delay window discriminator (Ellaway and Furness, 1983) was used to select the discharge profile of a particular motor unit. Each motor unit discharge triggered a 100 ms, +5 V pulse which was logged by computer. The muscles chosen for study were the extensor digitorum communis (EDC) of the forearm and the tibialis anterior (TA) of the leg. Subjects were asked to make a weak contraction of the muscle so as to recruit the discharges of motor units at both sites of electrode penetration. Audible feedback of the amplified discharges was provided to assist the subject to maintain a steady level of contraction during 1–2 min of recording. Recordings of the voluntary activation of motor units were made under conditions as close as possible to isometric contraction. However, some PD subjects showed difficulty in maintaining a steady level of contraction and recordings were made during overt tremor. Maximal voluntary contraction (MVC) of a muscle was not recorded for PD subjects, but it is estimated from a number of control recordings with normal subjects that the level of contraction used to record motor unit discharges for time series analysis was under 15% of MVC.

Time series analysis

Cross-correlation analysis was performed using a 1 ms time resolution up to ±100 ms or 120 ms from the time of each impulse in either of two trains of spikes over a period of, on average, 1–2 minutes. In some cases, the correlogram was extended up to ±400 ms if broad peaks or periodicities were suspected to be present. The location of any peaks or troughs in the correlogram, signalling a departure from the probability of discharge expected by chance, was judged by eye and by use of the cumulative sum derivative (cusum) of the correlogram (Ellaway, 1978; Davey *et al.*, 1986*c*). A central peak of brief duration (approx. ±5–10 ms), in an otherwise flat correlogram, was accepted as a statistically significant ($P < 0.001$) occurrence of short-term synchrony between the discharges of motor units (Sears and Stagg, 1976; Kirkwood *et al.*, 1982; Datta and Stephens, 1990) if the total number of counts in the n bins constituting the peak, as defined by the cusum, exceeded the counts expected by chance alone (nm) by more than $3.29 \sqrt{nm}$ where (m) is the mean count per bin in a control period (*see* Ellaway and Murthy, 1985*a*). A quantitative estimate of the increased probability of discharge of one motor unit, arbitrarily designated the event train, given a reference impulse in the discharge train of the other motor unit, was made according to the method described by Davey *et al.* (1987). This index of synchrony is given the abbreviation *XP*. A value of 0.1, for example, would indicate that on average, for the duration of the peak, one extra (above chance) event impulse occurred for every 10 reference impulses. In practice, the deviation from the expected probability of an event impulse given a reference impulse was calculated twice using each motor unit in turn as the reference. The reason for this is that an average value for the two motor units (Bremner *et al.*, 1991*a*) could be misleading when there exists a substantial difference in frequency of discharge of the two motor units. Both *XP* values are used in the presentation of data in the figures.

Regularity of discharge was computed as the coefficient of variation of interspike intervals (ratio of the standard deviation to mean interval). Time intervals between the spikes of individual neurons were measured and displayed as a sequential interval histogram. A stationary period of discharge was selected by eye and the mean and standard deviation of a sequence of not less than 30 intervals was calculated.

RESULTS

The study was based on 19 PD subjects (11 men, 8 women) ranging in age from 37 to 78 yrs (mean age 56.8 yrs) and 19 normal subjects (10 men, 9 women) ranging in age from 31 to 85 yrs (mean age 55.5 yrs). A discussion of the criteria used to select subjects appears in the Methods. The discharges of pairs of single motor units were obtained from the two muscles studies (EDC and TA) in all but two of the normal and four of the PD subjects. Multi-unit recordings were also obtained for time series analysis in some of these subjects and in a further 13 PD subjects.

Short-term synchrony

Cross-correlograms were constructed from the discharges of pairs of single motor units during weak isometric contraction of the muscle that was sustained for 1–2 min (*see* Methods). Correlograms for the group of 19 normal subjects either showed a central peak of the form seen in Fig. 1, or were featureless. The peaks, with a few exceptions, spanned time zero in the correlogram. Time zero represents the time of occurrence of the arbitrarily chosen reference motor unit spike (*see* Fig. 1). The width (time span) of the peaks showed considerable variation both between and within subjects. The mean (±1 SD) time spans for EDC and TA were 13.2±5.2 ms (range 2–25 ms) and

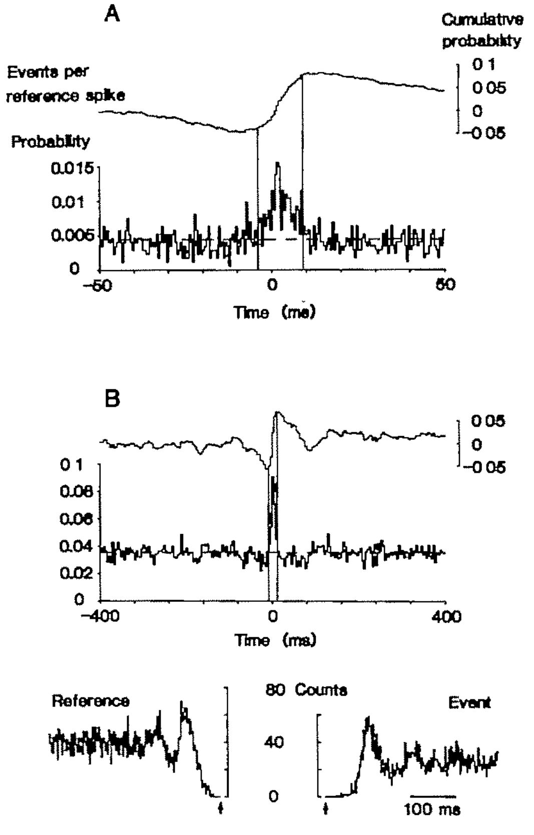

FIG. 1. Short-term synchrony in the EDC muscle of a normal subject. Correlation analysis for two motor units discharging during a weak isometric contraction. A, cross-correlogram (*below*) constructed from 1730 reference and 1376 event spikes using 0.5 ms bins over a period of 155 s. The horizontal dashed line is the mean expected count assuming no association between the spike trains. This mean value was used to construct the cumulative sum (*above*) of the correlogram. The ordinates have been expressed in terms of the probability (or cumulative probability) of discharge of one motor unit (event) given the discharge of the other (reference) at time zero. Vertical cursors delimit the correlogram peak The peak exceeds the distribution expected by chance alone ($P < 0.001$, *see* Methods). B, cross-correlogram and cumulative sum (*above*) from the same data, but using 4 ms bins. Autocorrelograms (*below*) for the two motor units. The autocorrelograms were constructed using 2 ms bins but are presented on the same time base as the cross-correlogram. The arrows mark the origins, or zero lag, of the autocorrelograms

10.3±3.4 ms (range 5–22 ms), respectively. Such peaks indicated a tendency to synchrony over the time span of the peak. It has been argued that peaks of this form, in correlograms of human motor unit discharges, are the result of the simultaneous occurrence of postsynaptic events caused by activity in branched last-order input axons (Datta and Stephens, 1990; Davey *et al.*, 1990; Nordstrom *et al.*, 1990). The amount and time course of synchrony of human motor discharges (Datta and Stephens, 1990) has been closely matched by the application of a theoretical model based on the joint occurrence of postsynaptic potentials (Kirkwood and Sears, 1978). The peaks are referred to as short-term synchrony, first described for cat intercostal motor units by Sears and Stagg (1976).

Figure 1 shows the autocorrelograms and cross-correlogram from the discharges of two motor units recorded in the EDC muscle of a normal subject. A pronounced peak of short-term synchrony spans time zero. The best estimate of the width of the peak was judged by eye as the extent of the clearly rising trend in the cumulative sum (Davey *et al.*, 1986*c*). Vertical cursors (Fig. 1A) have been used to mark the span of the peak of synchronization which amounts, in this case, to 13 ms. Inspection of the cross-correlogram and cusum suggests that the positioning of the cursors used to define the beginning and end of the peak in the correlogram may be rather arbitrary given the noisy nature of counts in the histogram. However, any error in determining the exact span of the peak has little effect on the measurement of the degree of synchronization. This measurement has been made by calculating the change (increase) in probability of firing of one motor unit with respect to the occurrence of a discharge in the other (Davey *et al.*, 1987). Previously (Ellaway and Murthy, 1985*a*,*b*) we have used the ratio (k′ value) of the integral of the counts in the peak to the expected count (between the cursors) but this index is sensitive to the exact position of the cursors.

For the data shown in Fig. 1A the probability of an event spike (in one motor unit) given a reference spike (in the other unit), over and above that expected by chance alone, was 0.117. That is, on average, there were 0.117 extra spikes within the time span (13 ms) of the peak for each discharge of the unit designated as the reference motor unit. This value may be read directly from the cumulative scale on the cusum in Fig. 1A. Alternatively, the index can be expressed using the previously designated event unit as the reference unit, in which case the value is 0.147. This alternative value is higher, simply because the newly designated reference unit has a lower frequency of discharge [8.7 impulses/s (ips)] than the previously designated reference unit (11.3 ips), but, of course, the total count in the peak is the same. Figure 1B presents the correlogram on a wider time base to show that the histogram is essentially flat outside the central peak except for slight dips up to approximately ±80 ms. These dips are the result of the rhythmic discharge of the motor units. They correspond approximately to the reduction in spike counts that is expected from the periodic nature of the motor unit discharge patterns seen in the autocorrelograms (Fig. 1C).

Short-term synchrony was readily identified for the discharges of motor units in PD subjects. However, correlogram peaks indicating short-term synchrony were obscured or distorted by broader correlations in some subjects. These broad correlations were caused by rhythmic fluctuations in discharge, with periodicity in the range 4–5 Hz, and are discussed later. The next sections compare short-term synchrony in normal and PD subjects.

Incidence of synchrony

Figure 2 presents the overall incidence of short-term synchrony detected during weak voluntary contraction for both EDC and TA for the 19 normal and 19 PD subjects. The variability within each group is evident and no clear difference between the two groups is apparent. The number of subjects showing more than 50% of motor unit pairs exhibiting synchrony was not significantly different for normal and PD groups (χ^2 = 2.4, $P > 0.05$). The data were tested again using only those subjects from whom at least five pairs of motor units were studied (14 normal, 17 PD), with the same result.

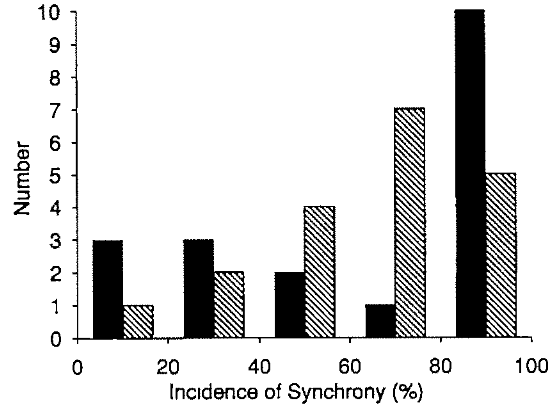

FIG. 2. The incidence of short-term synchrony in normal and PD subjects. The mean number of motor units studied in each case was eight for normal and 5 5 for PD subjects. Data for EDC and TA have been added together for each individual. Filled bars: normal subjects; hatched bars: PD subjects

In order to examine whether there was any difference in the incidence of synchrony for specific muscles, the total number of pairs of motor units exhibiting synchrony was assessed for EDC and TA, both in the normal and PD groups. In EDC, 66% of pairs (n = 77) in normal and 63% (n = 73) of pairs in PD subjects showed short-term synchrony. In TA the figures were 56% (n = 75) and 66% (n = 71), respectively. Chi-squared tests revealed no significant differences for the incidence of synchrony in the two muscles, or for the same muscle between the two groups of subjects.

Degree of synchrony

The amount of short-term synchrony varied considerably between different subjects both for the normal and PD groups. Figure 3 shows examples of strong, moderate and weak or absent synchrony in TA in normal and PD subjects. A similar range was observed for EDC in both groups. Table 1 documents the discharge parameters and correlation analysis for the subjects in Fig. 3. It can be seen from the variability in discharge rates in these examples that frequency of motor unit discharge is unlikely to be the cause of the gross differences in amount of synchrony for either normal or PD subjects. This point is elaborated upon later. In addition to inter-subject variability, the amount of synchrony between different motor unit pairs for a individual subject was also variable. The normal subject with the strongest synchrony in Fig. 3A showed synchrony between all pairs of motor units. The degree of synchrony (*XP* values) ranged from 0.03 to 0.15 (mean 0.07, n = 18 *XP* values, nine pairs). For comparison, the normal subject with

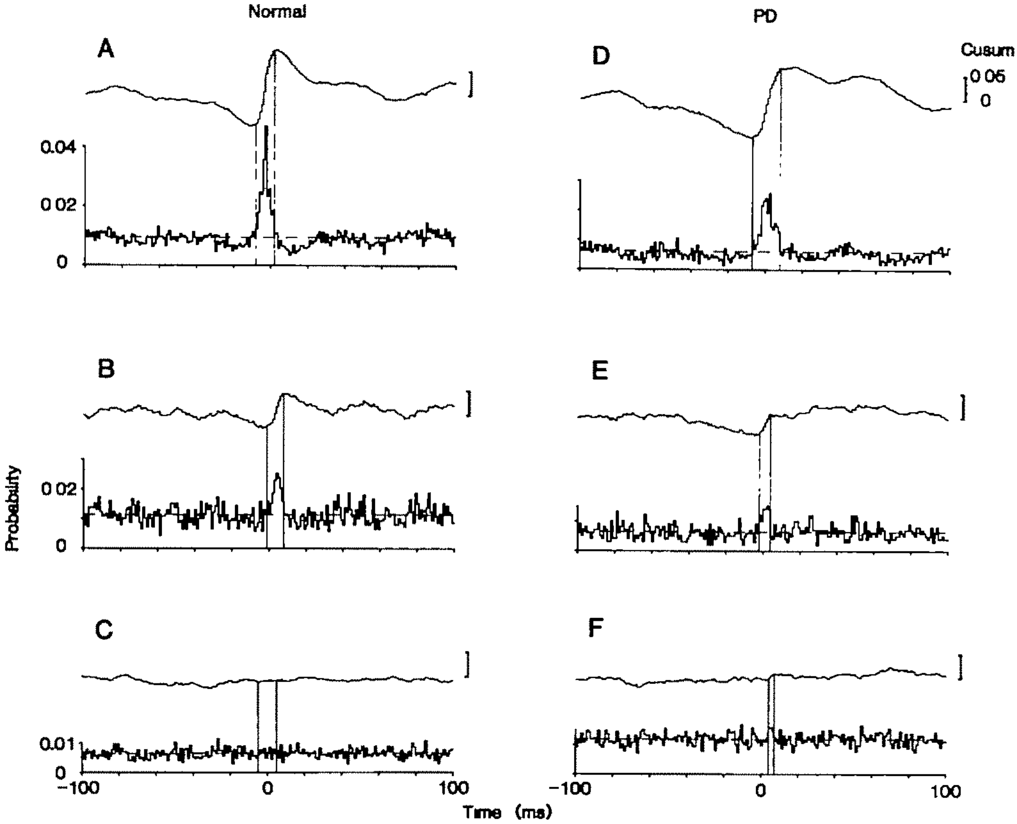

FIG. 3 Variability in the degree of short-term synchrony in normal and PD subjects. Correlation analysis of the discharges of pairs of single motor units during weak voluntary contraction of the TA muscle. Correlograms (*above*) and cusums (*below*) for three normal (A, B, C) and three PD (D, E, F) subjects were constructed using 1 ms bins The horizontal dashed lines (mean expected count) and vertical cursors are deployed as in Fig. 1, except in C where, in the abence of a peak, the vertical cursors are placed arbitrarily at ±5 ms

TABLE 1. CROSS-CORRELATION ANALYSIS OF NORMAL AND PD SUBJECTS

Subject[1] normal or PD	*Discharge rate (ips)*		*No of spikes in analysis (n)*		*Degree of synchrony[2] (XP value)*		*Width of peak in correlogram (ms)*
	Ref.	*Event*	*Ref.*	*Event*	*Ref.*	*Event[3]*	
A Normal	9.2	9.6	3947	4046	0.152	0.148**	10
B Normal	10.5	11.4	1382	1495	0.068	0.063**	9
C Normal	9.7	6.8	2693	1802	0.002	0.003 n.s.	10
D PD	8.9	7.6	1971	1430	0.143	0.197**	15
E PD	8.4	7.1	982	768	0.042	0.053**	6
F PD	13.0	12.5	2970	2684	0.011	0.012*	3

[1] The subjects A−F are those presented in Fig. 2 under the same labels. [2] The degree of synchrony (*XP* value) is expressed as the probability of a spike in the event train, given the occurrence of a reference spike, above that expected by chance alone, and vice versa. [3] The level of significance is indicated by the symbols **($P < 0.001$), *($P < 0.01$) and n.s. ($P > 0.05$, insignificant). They apply to both the reference and event *XP* values.

no apparent synchrony, in Fig. 3c, had no significant synchrony detectable for three pairs of motor units. However, synchrony was observed for six other pairs of motor units and the *XP* values ranged from 0.02 to 0.09 (mean 0.04, n = 12 *XP* values). Thus, although the degree of synchrony for any subject was variable, individuals performing the same motor task exhibited rather different average amounts of synchrony. The same was true for PD subjects.

Figure 4 shows the distributions of the synchronization index (*XP* value) for all pairs of motor units that exhibited statistically significant ($P < 0.001$) correlogram peaks of short-term synchrony. Two *XP* values have been calculated and plotted in Fig. 4 for each pair of motor units. Thus, for any record of motor unit discharge, each unit was used in turn as a reference unit to calculate an *XP* value (*see* Methods). The range of the *XP* index for EDC was remarkably similar for normal (0.015–0.17) and PD (0.025–0.165) subjects. The modal values were the same and there was no difference between the mean value for normal (0.07) and PD (0.07) subjects. In contrast, the synchrony index in TA tended to be higher for PD (range 0.040–0.215) than for normal subjects (range 0.016–0.150). In order to compare the two populations, each pair of *XP* values was averaged to provide a single index for a pair of motor units. The mean index for the PD group (0.091, n = 28 pairs of motor units) was found to be significantly different ($t = 4.3$, $P < 0.001$) from that of the normal group (0.058, n = 36 pairs). In particular, 61% of the *XP* values for the PD subjects were greater than 0.08 whereas this proportion was only 13% for normal subjects. Finally, for the normal group, there was no significant difference between the mean *XP* values of two muscles, EDC and

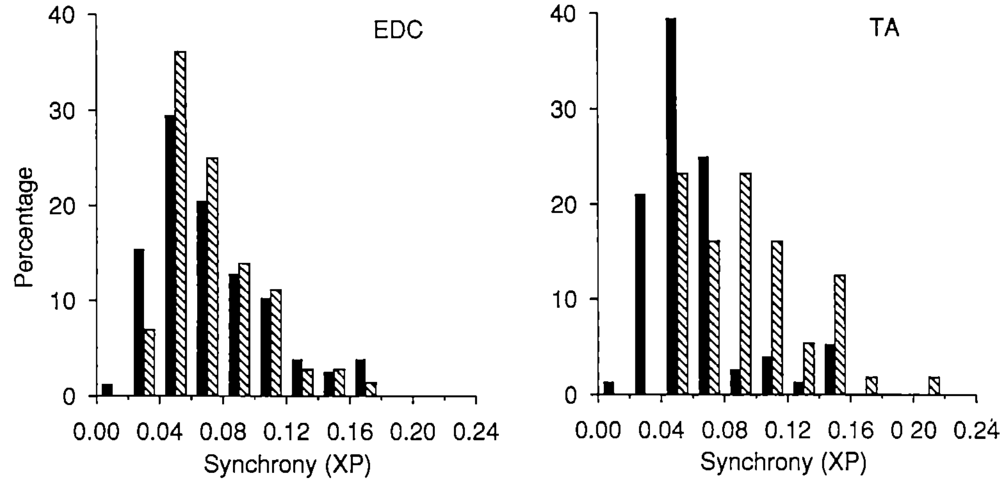

FIG 4. The distributions of the degree of short-term synchrony for motor units in normal and PD subjects during weak voluntary, isometric contraction. Left, data for EDC, right, data for TA; filled bars· normal subjects; hatched bars: PD subjects. Note the similarity of the distributions for normal and PD subjects for the EDC muscle, and the preponderance of high values of synchrony for PD subjects in the TA muscle

TA, whereas there was a significant difference between these two muscles in the PD group ($t = 3.7$, $P < 0.001$).

In addition to the index of synchrony, the widths of correlogram peaks, that is the span or duration of short-term synchrony, were compared for the two groups. There was no significant difference in mean durations between normal (13.2 ms ± 5.2 SD) and PD (13.3 ms ± 3.8 SD) subjects for EDC. However, as with the index of synchrony, the mean duration of synchrony for the PD group (13.6 ms ± 5.0 SD) was significantly greater than the normal group (10.3 ms ± 3.4 SD) in TA ($t = 3.2$, $P < 0.01$).

It was not possible to measure the degree of short-term synchrony in all the instances where it was detected. One reason for this was that short-term synchrony in PD subjects often occurred together with a periodic oscillation in the correlogram (*see later*). Under these circumstances it would have been difficult to ascertain the width and baseline of the peak of short-term synchrony and large errors in *XP* indices would have resulted. Visual inspection of correlograms with periodic oscillations suggests that a number of instances of a moderate to high degree of short-term synchrony have been omitted with the result that we have probably underestimated the amount of synchrony in the PD subjects. Another possible source of error in estimating the amount of synchrony in PD subjects arises from the fact that those with overt resting and postural tremor proved unsuitable for single motor unit study. Either they were unable to limit a voluntary contraction to the recruitment of a small number of motor units or adequate single unit analysis was thwarted by the bursting nature of the discharge that accompanied tremor. The thirteen subjects who fell in this category yielded 58 multi-unit recordings of which 67% showed clear evidence of short-term synchrony.

Synchrony and frequency of discharge

We have examined the possibility that the elevated synchrony for the TA in PD might be a consequence of lower firing rates of motor units. In the cat the amount of short-term synchrony between γ motor neurons (Ellaway and Murthy, 1985*a*) and α motor neurons (Connell *et al.*, 1986) is greater at lower discharge rates. This relation was not evident for motor units studied in man (Datta and Stephens, 1990) possibly due to the narrow band of frequencies encountered. In Fig. 5 the index of synchrony for statistically significant peaks has been plotted against the mean discharge rate of the reference motor unit calculated during construction of the correlogram. The plots suggest a weak negative correlation between synchrony and discharge rate. Regression analysis revealed the correlation to be significant in all but the case of the EDC muscle of the normal group. The question therefore arises as to whether the relative preponderance of high indices of synchrony for the TA in PD subjects is a result of lower discharge rates. Inspection of the graphs in Fig. 5 reveals that this is not the case. The *XP* values in excess of 0.08 for TA, of which there are considerably more for the PD compared with the normal group, are spread fairly evenly over the whole range of discharge rates. Furthermore, the range of discharge rates was similar for PD (2.7–12.8 ips) and normal (3.6–12.9 ips) subjects, and there was no significant difference between mean discharge rates (PD 8.5 ips, normal 8.6 ips, t test $P > 0.05$).

A similar assessment was made to examine any relation between width of the correlogram peak (duration of synchrony) and motor unit discharge rate. No significant

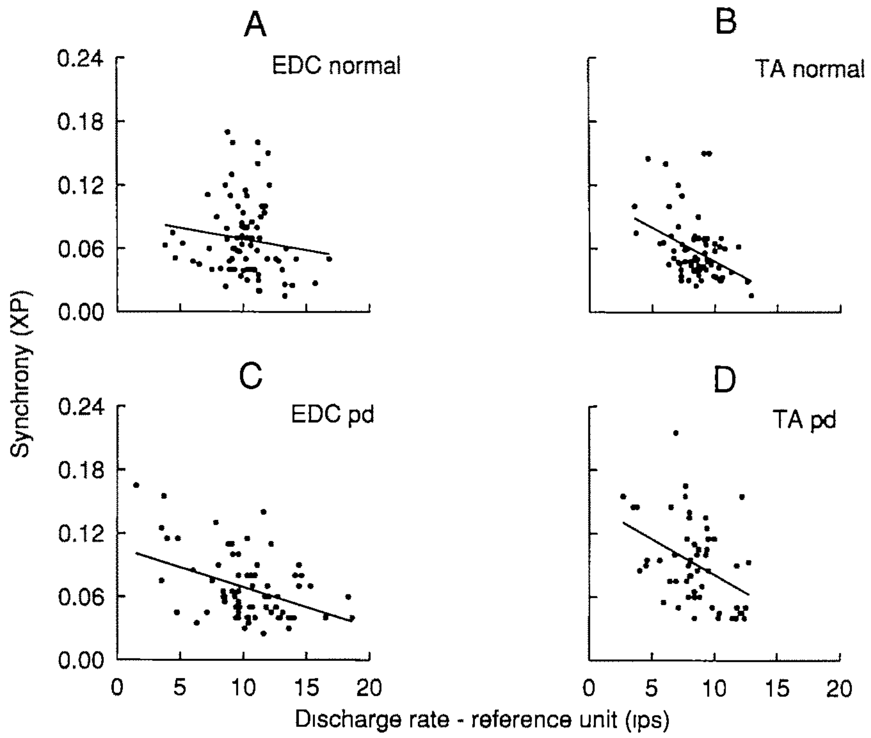

FIG 5. The relations between degree of short-term synchrony and motor-unit discharge rate. The degree of synchrony (*XP* value) has been calculated twice for each pair, i.e. with respect to each motor unit in turn as the reference unit, and plotted against the mean discharge rate of that reference unit. A, C, data for EDC muscles in normal (A) and PD (C) subjects. B, D, data for TA muscles in normal (B) and PD (D) subjects. Regression lines are superimposed on the data. The regression coefficients are significant ($P < 0.01$) in only three instances ($r = 0.39$ in B, 0.42 in C and 0.41 in D).

correlations were found between duration of synchrony and discharge rate for either of the two muscles in either normal or PD subjects. This was the case irrespective of whether discharge rate was taken as mean discharge rate of the pair of motor units, the lower or the higher discharge rate.

We conclude that the amount of short-term synchrony is elevated in PD disease for the TA but not the EDC muscle. This was not found to be a consequence of differences in firing rates of motor units which were spread over a similar range in the normal and PD groups.

Periodic correlations

In a number of PD subjects periodicity appeared in the correlograms constructed during a sustained isometric task. Figure 6 shows correlograms from two subjects in whom periodicity was detected. The correlograms constructed on a time base of ±100 ms show simply a broad based peak. However, on the longer time base of ±400 ms it can be seen that these correlations are periodic and have frequencies close to 5 Hz (4.6 and 4.7 Hz). Seventeen PD subjects overall, mainly from the multi-unit group, showed

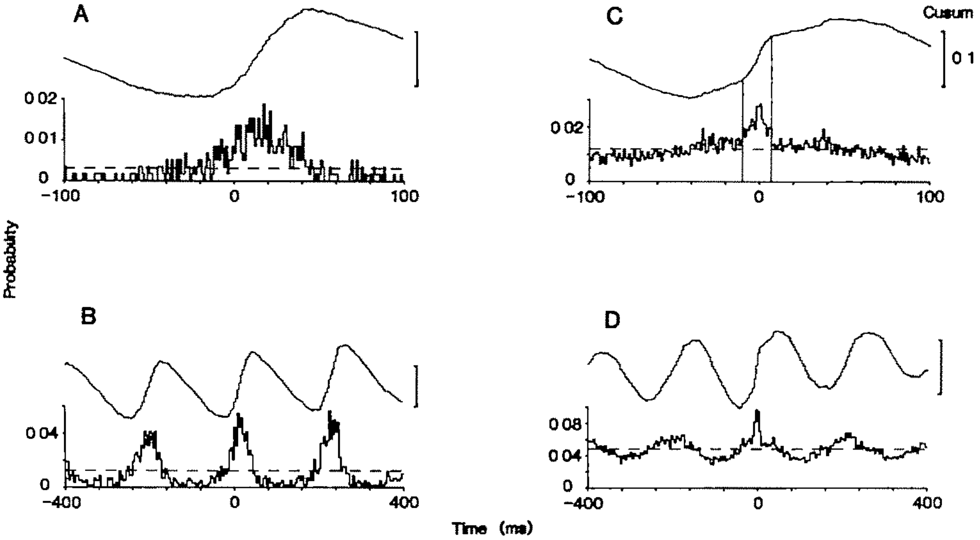

FIG. 6. Broad periodicity at 4–5 Hz in the cross-correlograms from pairs of single motor units in PD. Two subjects (A, B and C, D) are presented with a correlogram for each subject presented both on a short (A and C) and long (B and D) time base, respectively. Note that the broad correlations seen in A and C repeat at regular intervals in the correlograms on a long time base (B and D) and indicate periodic firing of the motor units. In addition to the periodicity, one subject (C, D) also exhibits short-term synchrony, delimited by the vertical cursors in C, and evident as a discontinuity in the periodic rise and fall in counts in D The correlograms were constructed from 582 reference and 435 event spikes over 100 s (A, B) and 3946 reference and 4659 event spikes over 380 s (C, D).

periodicity. Both muscles were frequently affected. The frequencies of 24 instances of periodic fluctuations ranged from 4.2 to 10.3 Hz but 20 of these fell in the range 4–6 Hz. Thus the range covered frequencies associated with both rest and postural or action tremor of PD (Findley *et al.*, 1981). In contrast with the PD group only three of the 19 normal subjects showed periodicity. The frequency of the periodicity ranged from six to 11 Hz but was weaker than for PD subjects. Furthermore, in each instance the discharge rates of the two motor units and the frequency of the periodicity were very similar, which was not generally the case for the PD group. For example, the periodicity in the correlogram of Fig. 6B has a freuqency of 4.7 Hz whereas the rates of motor unit discharge were 10.6 and 12.0 ips. Equivalent values for a normal subject were a periodicity of 7.3 Hz and discharge rates of 7.3 and 7.9 ips. Thus, the periodicity in the normal subjects may result from chance beating of impulse trains of similar rates.

Broad based, but aperiodic, correlogram peaks (widths >40 ms) have been observed for the discharges of intercostal motor neurons and were thought to arise from non-rhythmic but synchronized activity in presynaptic interneurons (Kirkwood *et al.*, 1982). Synchronized presynaptic activity is less likely to be responsible for the wide, correlogram peaks seen in our PD subjects since the correlations were periodic. The periodicity suggests that a rhythmic drive is present in the presynaptic input neurons. A similar proposal was made by Kirkwood *et al.* (1982) as the basis for high frequency oscillations (60–120 Hz) observed in the correlograms of intercostal motor neuron discharges. The periodic nature of motor unit discharges at frequencies typical of PD tremors (5 Hz) is thought to arise from a loosely correlated supraspinal drive of thalamic origin (Albe-Fessard *et al.*, 1963; Jasper and Bertrand, 1966; Ohye *et al.*, 1974). The broad based, periodic correlations seen in this study had rhythmic frequencies close to 5 Hz and were often, but not invariably, accompanied by overt postural tremor in the PD subjects.

In many instances where a periodic correlation was observed between two motor units in PD subjects a narrow peak could clearly be seen protruding from the broad central peak. The correlogram in Fig. 6B is a typical example. These narrow peaks were only ever observed around the time of discharge of the referenced unit, i.e. time zero in the correlogram. Narrow peaks did not occur in association with other periodic increases in probability of discharge away from the time of reference unit discharge. We interpret them as being instances of short-term synchrony, arising from activity in common presynaptic stem fibres, combined with the 4–5 Hz periodic drive to the motor neurons of supraspinal origin. In many instances the narrow peak of short-term synchrony merged almost imperceptibly into the broad peak. In these cases the presence of short synchrony could only be inferred by noting that the peaks at one, two or more periods from the central peak were all similar in size but smaller than the central peak. It was not possible to measure the degree of short-term synchrony in any of the correlograms showing periodicity since the central peak could not be clearly delineated either in width or depth. Thus, none of these instances of short-term synchrony have contributed to the values in Fig. 4. Since some of these peaks were quite substantial we feel that this restriction has caused us to understate the degree of the short synchrony in PD.

Doublet discharges

One other characteristic of motor neuron discharge that was frequently observed was the occurrence of short intervals or doublet discharges. In the case of normal subjects these doublets had short interspike intervals in the range 5–15 ms (mean = 7.9 ms). They were observed in eight out the 19 subjects but were evident only for a small proportion of motor units in each individual. The doublets formed only a small fraction of the discharges during recording sessions made while subjects maintained a steady level of contraction. Eight PD subjects also showed doublets but these fell into two distinct categories. Seven showed doublets with short interspike intervals (range 4–8 ms, mean 6.4 ms) and a low incidence similar to that of normal subjects. Four other PD subjects showed a tendency for motor units to discharge alternate short and long interspike intervals with short intervals in the range 20–66 ms (mean = 47.6 ms). The pattern is evident in the auto- and cross-correlograms of Fig. 7. In this PD subject the interspike intervals of the two motor units were similar. The principal short and long interspike intervals for the two units were, on average, 40 and 140 ms. This gives an overall repeat interval of 180 ms which is equivalent to a rate of 5.5 Hz. The cross-correlogram on the short time base in Fig. 7A shows a broad correlation with side peaks associated with the short-interval discharges. On a longer time base (Fig. 7B) it can be seen that the correlation is periodic in nature with a frequency of 5.4 Hz. It is impossible to gauge whether short-term synchrony is contributing to the discharge patterns. On all occasions that alternating short and long intervals were observed, correlograms showed a periodic correlation in the frequency range 4.1–5.6 Hz.

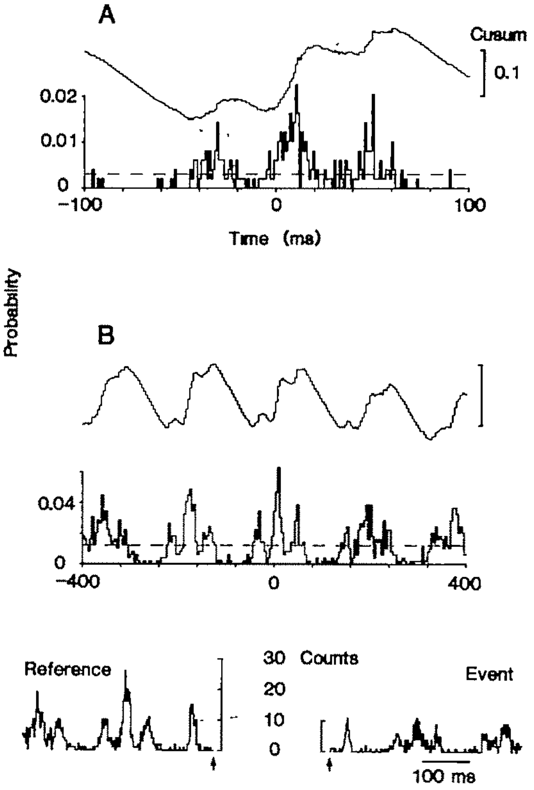

FIG. 7. Doublet discharges and periodicity at 5.5 Hz of motor units in PD The correlograms in A and B have been constructed from a 64 s discharge using the same 490 reference spikes with 1 ms (A) and 4 ms (B) bin widths. The autocorrelograms for the two motor units were constructed using 2 ms bins, and the origins (zero lag) marked with arrows. A, cross-correlogram (*below*) and cumulative sum (*above*) show three broad peaks reflecting the cross-correlation of doublet discharges of the motor units B, cross-correlogram (*centre*), cumulative sum (*above*) and autocorrelograms (*below*) for the same data. The discharges are revealed as periodic with both motor units firing doublets having interspike intervals of approximately 40 ms and longer intervals of 140 ms. The lower total spike counts in the autocorrelogram indicates that the 'event' unit failed to discharge as often as the 'reference' unit, but otherwise fired in phase.

Synchrony and L-dopa

In four PD subjects we attempted to assess the amount of short-term synchrony before and after they took L-dopa in the form of Siemet (Merck, Sharp and Dohme). One newly diagnosed subject was examined before (OFF) and after (ON) starting medication for Parkinson's disease. All four pairs of motor units in EDC in the OFF state showed short-term synchrony and the index of synchrony ranged from 0.04 to 0.07. In the ON state, again all pairs ($n = 5$) in EDC showed synchrony and with a similar range of the *XP* index (0.04–0.08). The correlograms for TA in this subject showed periodic fluctuations in both the OFF (5.1 Hz) and ON (4.9 Hz) states. Strong short-term synchrony was evident in both states but, due to the periodicity, it was not possible to measure the peaks for comparison. Three further subjects were observed immediately before taking their normal L-dopa prescription (Sinemet+) and approximately 3–4 h since their previous medication. Neither as indivdiuals nor as a group were any clear differences in the amount of short-term synchrony observed before and after L-dopa. The mean values of the index of synchrony for EDC were 0.054 (±0.015 SD) before and 0.048 (±0.016) after, and for TA, 0.107 (±0.052) before and 0.123 (±0.057) after L-dopa therapy. For neither muscle were the differences significant (*t* test) at the 5% level.

DISCUSSION

The principal aim of this study was to investigate whether the amount of short synchrony of discharge between motor units in PD differs from that in normal subjects. In order to make this assessment it has been necessary first to establish that there is an equivalent basis for comparison, particularly with regard to discharge rates.

We find for both normal (n = 19) and PD (n = 19) subjects that, on average, 30–40% of pairs of motor units in both EDC and TA lack short-term synchrony. Another report on five normal subjects has found that synchrony is invariably present for TA, but not for gastrocnemius medialis (Datta *et al.*, 1991). We do not think that we have overlooked peaks in correlograms in our study since the cumulative sum technique is such a sensitive indicator of change. However, we have required correlogram peaks to achieve statistical significance at values of $P < 0.001$ for positive identification of short-term synchrony. A lower level of $P = 0.01$, such as the putative correlogram peak in Fig. 3F, is not convincing as an instance of short-term synchrony. Peaks (or troughs) that amount to a significant departure from the expected level at the 1% level of significance ($P = 0.01$) are going to be a frequent feature of correlograms consisting of 200 bins. One caveat concerns our PD data. The number of spikes contributing to the correlogram in PD subjects was sometimes lower than for normal subjects because the subject could not maintain a steady voluntary contraction. If peaks were missed due to low counts in the correlogram then the incidence of short-term synchrony would be higher for the PD group than the normal group. However, the distribution of *XP* values in Fig. 4 (amount of synchrony) would then show a higher proportion of low values, assuming that these correlograms would have peaks barely reaching significance. Even so, a considerable proportion of *XP* values would remain greater than 0.08 for TA in PD, which is not the case for normal subjects.

A second factor that could erroneously lead to the conclusion that short-term synchrony was greater for one group than another arises from the expectation that the amount of synchrony increases at lower discharge rates (*see* Ellaway and Murthy, 1985*a*). However, motor unit studies in man (Bremner *et al.*, 1991*b*) have revealed no consistent relation between synchrony and firing rate. In the present study a weak negative correlation between synchrony and discharge rate was oberved both for EDC and TA muscles. However, it was clear from inspection of the graphs (Fig. 5) that the strength of the relation was far too low to account for the relative preponderance of high synchrony values in the TA muscles of PD subjects. Although it has been reported that motor units discharge at slower rates in PD (Dietz *et al.*, 1974) this was not a general finding for those discharge trains where short-term synchrony was evident. The mean rates of discharge in these cases, for EDC and TA, respectively, were 10.2 and 8.6 ips for normal and 10.1 and 8.45 ips for PD subjects. There was, therefore, no evidence in the present study that the higher indices of synchrony in TA muscles in the PD group were a result of lower discharge rates. Motor unit discharge rates in PD subjects were often observed to be lower than for normal subjects but these instances tended to give rise to periodic correlograms in which short-term synchrony was either absent or, possibly, obscured.

Since there is some evidence that the amount of synchrony during voluntary contraction in normal subjects depends upon the muscle in use (Datta *et al.*, 1991) we have compared the two muscles used in this study. In our normal subjects neither the incidence nor the degree of synchrony were significantly different between the forearm (EDC) and leg (TA) muscles. Neither were there differences between the EDC muscles of normal and PD subjects. The situation was, however, different for the TA muscle. Here, although the incidence of short-term synchrony in PD was not different from that seen in normal, age-matched subjects, the amount of synchrony as assessed by the *XP* index was significantly greater in the PD subjects. We take this to imply either, that the number of shared inputs or synaptic efficacy is greater in PD, or that voluntary contraction of TA in PD involves a greater amount of activity in shared presynaptic stem fibres than is the case in normal man. We argue below that this may reflect a disorder of descending bulbospinal inhibition in PD. However, an alternative reason for the increased synchrony in PD could be a reorganization of the drive to motor neurons during voluntary contraction of the TA muscle. The only feasible alternative would be an increase in synchrony of the activity in the different neurons constituting the supraspinal drive. Any synchrony arising as a result of drive in a group of presynaptic neurons that are themselves synchronized would be expected to broaden the correlogram peaks from the discharges of the postsynpatic motor neurons (Kirkwood *et al.*, 1982). The mean width of peaks for TA was slightly greater in PD (13.6 ms) than normal (10.3 ms) but the ranges were 5–22 ms and 4–24 ms, respectively, and overlapped substantially.

Broader correlations were observed for some PD subjects but, in almost all instances, inspection of the correlograms on a long time base revealed that these were part of a periodic correlation that represented low frequency entrainment of motor units. The periodicity had a frequency in the range 4–6 Hz and reflected the tremor that often accompanied the isometric task performed by the subject. These frequencies are in the range previously reported as typical of PD tremors (Lance *et al.*, 1963; Stiles and Pozos, 1976) although a distinction between postural (around 6 Hz) and rest tremor (4–5 Hz) is generally accepted (Findley *et al.*, 1981; Marsden, 1984). In our recordings some PD subjects, and possibly a few normal subjects, although instructed to recruit motor units and maintain their steady discharge rate during an isometric contraction, were in a state indistinguishable from resting conditions. For example, the motor units being assessed for short-term synchrony sometimes continued to discharge at the end of the recording session when the subject was instructed to cease the isometric contraction.

It is generally accepted that lesions of the ventral medial tegmentum that destroy dopaminergic neurons arising from the pars compacta of the substantia nigra, give rise to tremor typical of PD (Poirier *et al.*, 1966, 1969) and that the tremor may be driven by neurons of the ventral lateral thalamus (Guiot *et al.*, 1962; reviewed by Ohye, 1982). Furthermore, reflex mechanisms do not seem to be involved in the tremor of PD (Lee and Stein, 1981). The evidence for a central origin of PD tremor in the basal ganglia and thalamus is so strong that little attention has been given to the possibility that disorder elsewhere in the nervous system in PD may contribute to the motor dysfunction. One contribution to tremor might be expected to arise from synchronization of motor unit discharges at the level of the spinal cord given the tendency of motor neurons to discharge at similar, steady rates (Taylor, 1962; Allum *et al.*, 1978). It is relevant therefore to speculate whether the increased amount of short-term synchrony that we have observed for TA in PD subjects is a result of a disordered bulbospinal system and whether it contributes to tremor. In PD it is known that monoamine levels are abnormal in the spinal cord (Scatton *et al.*, 1984). In the cat we have shown that a descending monoaminergic pathway in the dorsolateral funiculus, arising from a subcoerulear region, limits the amount of short-term synchrony (Davey and Ellaway, 1988; Baker *et al.*, 1991). The pathway presumably acts by inhibiting segmental or descending inputs in shared presynaptic fibres to motor neurons (Rudomin *et al.*, 1975; Kirkwood *et al.*, 1982). Thus the increased synchrony in PD subjects may reflect a disordered bulbospinal system that normally would inhibit certain synchronizing influences from segmental and descending inputs to motor neurons. However, it is not clear why a similar abnormality has not been seen for the forearm muscle EDC. Most subjects were examined while receiving L-dopa therapy but the amount of synchrony was not noticeably changed in one subject after going onto L-dopa for the first time. Neither was synchrony clearly different in the three subjects examined at a trough in their medication. However, the conclusion that L-dopa does not influence the amount of synchrony must remain tentative since only a few subjects were examined and, of course, the motor unit pairs were not the same in the two recording sessions.

Two features of motor unit discharge is seen in our PD subjects which were not observed in normal subjects. They were the periodic correlations at 4–6 Hz and the double discharges of longer interspike interval (20–66 ms). Doublet discharges of short-interspike interval (5–15 ms) are not regarded as pathological (Kudina, 1974; Bawa and Calancie, 1983) and indeed were observed for eight of our 19 normal subjects, although infrequently in terms of the proportion of discharges by individual motor units. The longer doublets have previously been described in PD and may be expected to contribute to tremor through the nonlinear twitch summation properties of motor units (Dengler *et al.*, 1990). In our experience these double discharges were associated with periodic correlograms. Thus, the double discharges would be accentuating the tremor caused by the periodic grouping of motor unit discharges at 4–6 Hz. The presence of short-term synchrony and, in particular, the instances of excessive synchrony in the TA muscle of PD subjects were not linked to those instances where motor units showed strong periodic discharges. Although it is possible that we may have underestimated the degree of short-term synchrony in PD subjects, as a result of narrow peaks being obscured by the broad correlations of the periodic discharges, short-term synchrony clearly was not present in certain instances when slow frequency (4–6 Hz) periodicity was observed. Thus, while the amount of short-term synchrony is clearly greater for TA in PD we feel that it is broad, periodic correlation rather than short-term synchrony that contributes to the typical rest or postural tremor of PD subjects.

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IMPAIRED NON-MOTOR LEARNING AND ERROR DETECTION ASSOCIATED WITH CEREBELLAR DAMAGE

A SINGLE CASE STUDY

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SUMMARY

A previously conducted positron emission tomography (PET) study of normal humans suggested that the cerebellum makes important non-motor contributions to language processing. Beginning with the task which produced right cerebellar PET activation, we studied a 49-yr-old male (RC1) with right cerebellar damage on a variety of tasks involving complex non-motor processing Whereas RC1's performance on standard tests of memory, intelligence, 'frontal function' and language skills was excellent, he had profound deficits in two areas. (1) practice-related learning; (2) detection of errors. Considered in relation to cerebellar contributions to motor tasks, the results suggest some functions performed by the cerebellum may be generalized beyond a purely motor domain.

INTRODUCTION

The hallmarks of cerebellar damage or degeneration are motor impairments. These have been reported for over 100 years (Dickinson, 1865; Jackson, 1932). Typical symptoms include gait ataxia, dysmetria, dysarthia and vertigo (Holmes, 1939; Gilman *et al.*, 1981). Not surprisingly, both human and animal investigations of the cerebellum have concentrated on understanding the cerebellar functions which underlie these motor disturbances (e.g. Thach, 1970; Mano, 1974). Only fairly recently has it been suggested that the cerebellum may have important non-motor functions. Several investigators have identified cerebellar hypoplasia in individuals with autism (Bauman and Kemper, 1985; Gaffney *et al.*, 1987; Murakami *et al.*, 1989). Reviews of the cerebellum by both Watson (1978) and Berntson and Torello (1982) conclude that the cerebellum is involved in some emotional processes, such as motivation and reinforcement. Leiner *et al.* (1989), in one of a series of articles on the topic, concluded, 'recent behavioral evidence indicates that the human cerebellum is involved in a wider range of functions: in learning, in planning, in judging time, in some emotional and cognitive disorders such as autism, and in some normal mental activities such as the cognitive processing of words'.

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Claims that the cerebellum contributes to cognitive functions are largely based on anatomical connections and phylogenetic development. The more recently evolved neocerebellum, which consists primarily of the lateral hemispheres and dentate nucleus, may be ideally suited to deal with high-order tasks involving cortical processing (reviewed by Leiner *et al.*, 1986). Phylogenetically, neocerebellar growth has paralleled that of the frontal cortex (Dow, 1942). Input into the neocerebellum is predominantly cortical, via cortical terminations in the pontine and olivary nuclear regions which project to neocerebellar structures (Dow, 1942). Neocerebellar efferent cortical projections are relayed through the thalamus primarily to motor areas, though there is evidence that in higher primates output may extend further frontally (Sasaki *et al.*, 1979; Asanuma *et al.*, 1983; Miyata and Sasaki, 1983).

Only a limited amount of behavioural evidence in humans, and none in other primates, is available to support claims that the cerebellum has important non-motor functions. Ivry and Keele (1989) studied patients with Parkinson's disease, cerebellar damage, cortical damage and peripheral nerve injury on two different tests of timing functions: the first measured the ability of subjects to produce and maintain a simple rhythm, and the second measured the ability of subjects to discriminate differences between interval durations. The cerebellar group showed deficits in both timing production and perception. Bracke-Tolkmitt *et al.* (1989) studied five patients with either cerebellar lesions or atrophy using a battery of standard neuropsychological tests. Compared with age- and education-matched controls, the patients were impaired on verbal, spatial and general ability intelligence measures. Patients also performed significantly poorer than controls on a verbal paired asssociates test, and a conditional associative learning task in which the subjects had to learn, by trial and error, arbitrary associations between six words and six colours. The patients were not significantly impaired, relative to controls, on most tests of memory (e.g. digit span, delayed recall of stories, etc.), or on the Wisconsin Card Sorting Test. Studies of cerebral blood flow and metabolism in normals have recently shown increased cerebellar activity during tasks in which subjects are instructed to imagine motor movements (Decety *et al.*, 1990), and during the learning as compared with recognition phase of a task requiring tactile discrimination of complicated geometrical objects (Roland *et al.*, 1989).

Our interest in the cerebellum was stimulated by a PET study of language processing previously conducted in our laboratory. As part of this study, subjects were asked to think of and say aloud appropriate verbs for presented nouns. During the control scan, subjects were asked merely to read aloud presented nouns. Unexpectedly, activation of a right lateral cerebellar region was found when subjects generated verbs, but not when they repeated nouns. This activation was clearly distinct from more medial and bilaterally-activated cerebellar regions found during both verb generation and noun repetition. The activation was found regardless of whether the nouns were presented auditorily or visually. In addition to the cerebellar activation, a set of left-lateralized cortical regions was activated during the verb generation but not noun repetition task. This correspondence (the cerebellar hemispheres receive contralateral cortical input), as well as the lack of lateral cerebellar activation during simpler verbal output tasks, made it difficult to account for the cerebellar activation on a purely motor basis (Petersen *et al.*, 1989).

SUBJECTS

Patient case report

A 49-yr-old right-handed male lawyer with a history of systemic hypertension suffered a sudden onset of nausea, vomiting, intense vertigo, and loss of motor control. Subsequent to his hospital admission, he complained of bifrontal headache, residual vertigo and a mild and difficult to describe visual problem with reading. MRI and CT examination revealed an extensive right-lateralized cerebellar infarct in the distribution of the right posterior inferior cerebellar artery, with no other visible brain abnormalities (*see* Fig. 1).

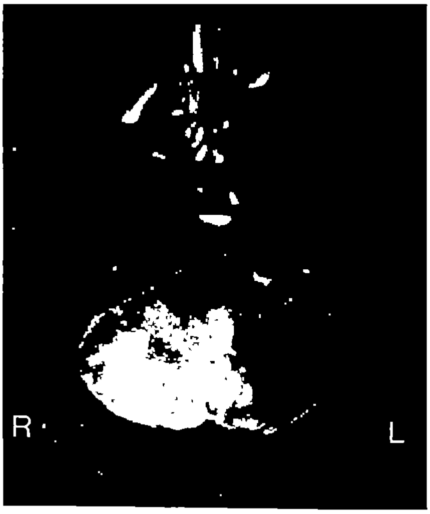

FIG. 1. Horizontal MRI section from patient RC1 showing extensive right cerebellar infarction.

Neurological examinations revealed a smaller right pupillary size as compared with the left. Muscle tone was felt to be slightly decreased in the right arm as compared with the left. Finger-nose-finger testing on the right side revealed a mild degree of ataxia. The remainder of the segmental neurological examination was normal. The patient was discharged 2 wks after his stroke without significant deficits noted by neurologists, and he soon resumed his private law practice on a full-time basis. Twelve months after his stroke, the patient died suddenly and unexpectedly from natural causes. No autopsy was performed. The patient will be referred to as RC1, an abbreviation for the location of his lesion.

Six months after his stroke, RC1 self-reported few remaining problems. He noted occasional episodes of vertigo, which most often followed a rapid head rotation; a decrease in the legibility of his handwriting, most noticeable when writing quickly; a diminished ability to make precise shots in pool, an increased incidence of 'slips of the tongue' (which, based upon his self-explanation, appeared to be semantic paraphasias); a decline in his 'instant recall abilities', e.g. the ability to instantly associate the clients' names with details of their cases; and a shortened attention span, which he attributed to his cessation of smoking. When questioned, RC1's wife also mentioned his 'slips of the tongue', but did not report any other problems or changes in his personality.

RC1 was tested acutely one and a half weeks after his stroke, and subsequently 2, 6, 9 and 10 mths later. Since RC1 did not show marked changes in his performance, the results will be discussed without reference to the date of testing. Informed consent was obtained prior to all testing sessions.

Control subjects

Three right-handed male subjects were used as controls for RC1. In addition to sex and handedness, they were matched for age, education and intelligence (*see* Table 1). Control subjects participated in two

3.5 h testing sessions, with 1–7 d between sessions. Informed consent was obtained from each control prior to both testing sessions. The order of tests was the same for all of the controls.

EXPERIMENTAL INVESTIGATIONS: METHODS AND RESULTS

Equipment, stimulus display and materials

All reacton time tests were administered using a Macintosh IIx computer system for controlling stimulus display and data acquisition. Unless otherwise noted, an electronic circuit (a voice-key) gated by the amplitude of a microphone input was used to measure voice onset times for verbally produced responses. Responses were also recorded onto a cassette tape. Non-verbal responses were made by pressing one of two designated keys on a standard ASCII keyboard. Stimuli were displayed in upper-case letters beneath a 3×3 mm cross-hair centred on either an Apple high resolution RGB or monochrome monitor. All words were open-class words with a frequency greater than five occurrences per one million words (Kucera and Francis, 1967). Pattern stimuli were adapted from Raven's Standard Progressive Matrices (Raven, 1956).

General abilities

On the basis of routine social interactions, RC1 appeared perfectly normal and unimpaired. As a means of more formally testing RC1's general level of performance, standard tests of language, memory, intelligence and 'frontal function' were administered. The results are listed in Table 1. RC1's scores on Wechsler Adult Intelligence Scale, Revised (WAIS-R) (Wechsler, 1981), Wechsler Memory Scale, Revised (WMS-R) (Wechsler, 1987) and Wisconsin Card Sorting Test (Heaton, 1981) were above average to superior. His score on the Picture Arrangement subtest of the WAIS was perfect, and his performance was rapid: he solved 8 out of 10 of the picture arrangement problems in less than half of the allowable time. On the Boston Diagnostic Aphasia Exam (Goodglass and Kaplan, 1983), RC1 appeared to have greater than average difficulty on an oral manipulation subtest, though his performance was in the acceptable range. Apart from

TABLE 1 INCLUSION CRITERIA AND PERFORMANCE ON STANDARD TESTS OF MEMORY, LANGUAGE AND FRONTAL FUNCTION

Inclusion criteria/performance	*RC1*	*Controls*
Inclusion criteria		
Handedness	R	R
Age	49–50	48±5 SD
Years of education	17	16±0 SD
Intelligence quotient (WAIS-R)	131*	133*±4 SD
Memory		
Memory quotient (WMS-R)	124*	131*±1 SD
Digit span	6	6±0 SD
Tapping span	8	7±1 SD
Delayed match to non-sample	60/60*	
Language		
Boston Diagnostic Aphasia Exam	Spelling error	
Boston Confrontation Naming	60/60*	
Token Task	No errors	
Frontal		
Wisconsin Card Sorting Test	5 errors* (6 categories)	
Picture Arrangement	20/20*	16*±4
Word fluency ('CFL' test)	42 words	66, 45, 44

* = above-average performance according to population normals.

this observation, no evidence for any impairments was found across several diagnostic tests for language disorders (Kaplan *et al.*, 1983; Lezak, 1983).

Rule-based generation tasks

Since our interest in the cerebellum was motivated by our observation of cerebellar activity during a verb generation task, we began our investigations of RC1's deficits by asking him to perform a version of this task while he was still in the hospital. Following this initial testing, RC1 was subsequently tested on a variety of other rule-based generation tasks, in order to determine whether deficits noted initially were stable and limited solely to verb generation.

Verb generation

Methods. Two practice blocks were used to determine an appropriate rate of presentation, and then RC1 was presented with a new list of 40 high-frequency concrete nouns, at a rate of one every 2.2 s. He was asked to produce an appropriate verb for each noun. RC1 was told his answer should be an action word which described what the presented noun might do, or what it might be used for. The same list of nouns, in a different random order, was then presented for five more blocks, to give a total of six blocks with the same list. The instructions were repeated and the importance of speed stressed several times between blocks. For the seventh block, RC1 was asked to read aloud 80 nouns.

To measure both reaction time and response durations, RC1's responses were recorded onto one track of a cassette tape, and a brief tone inaudible to RC1 and synchronized to the onset of stimulus presentation was recorded directly on the second track of the cassette tape. Using a Macintosh IIx computer and MacRecorder software, the tape was digitized and amplitude envelopes were obtained for each response. Reaction times and response durations were calculated by measuring the latencies between tone and response onsets and response offsets.

Control subjects were given the same instructions and block sequence, and words were presented using identical display and rate parameters, as well as order of presentation. Reaction times were determined using a voice-key to measure voice-onset times.

Results. RC1's simple naming speed was slower than that of controls: his median reaction time for reading aloud the nouns presented in block 7 was 642 ms, over 2.5 standard deviations above the mean of 513 ms for controls. However, RC1's median reaction time for verb generation in block 1 was 1045 ms, within the range of control values (mean for controls was 1161 ms ± 348 SD). Most importantly, while all three controls showed a significant 3.9 to 7.5% reaction time decrease per block ($P < 0.015$ for all controls, simple linear regression), RC1 did not show a significant correlation between reaction time and block (slope = 1% decrease per block, $P = 0.38$, simple linear regression). Results are shown graphically in Fig. 2.

In addition to his learning deficit, RC1 also produced an abnormally high number of non-verb associates for the presented nouns. For instance, whereas normal subjects usually respond to the noun 'razor' with the verb 'shave', RC1 said 'sharp'. Further examples are given in Table 2, which lists responses given by RC1 for the first 25 nouns presented in block 1. For comparison, the responses of the first control subject tested and the most common response to each noun are also listed. The typicality of responses made by RC1 and control subjects were evaluated by comparison with a corpus of responses generated by other subjects. A response was defined as atypical if none of 35 previous subjects had generated the same answer. Results are shown in Fig. 3. Controls averaged 13% atypical responses across all blocks of the task. RC1, on the other hand, peformed more than eight standard deviations above the control mean, averaging 55% atypical responses; furthermore, he showed no tendency to correct his 'errors' across blocks (0% decrease in errors per block, $P = 0.93$, simple linear regression).

Other rule-based generation tasks

Method. The method used for the verb generation task was modified so that the rate of stimulus presentation was paced by each subject. Each word remained on the screen until either a response was made or 9 s had elapsed since the initial presentation of the word, at which point the word was erased. Following a 1.5 s intertrial interval, during which only a central cross-hair remained on the screen, the next word was presented.

For each of the generation tasks, subjects were given a particular rule by which they were to generate a response to each presented word. In order to ensure subjects understood each task, they were given three practice trials with feedback about the correctness of their responses. Following the three practice

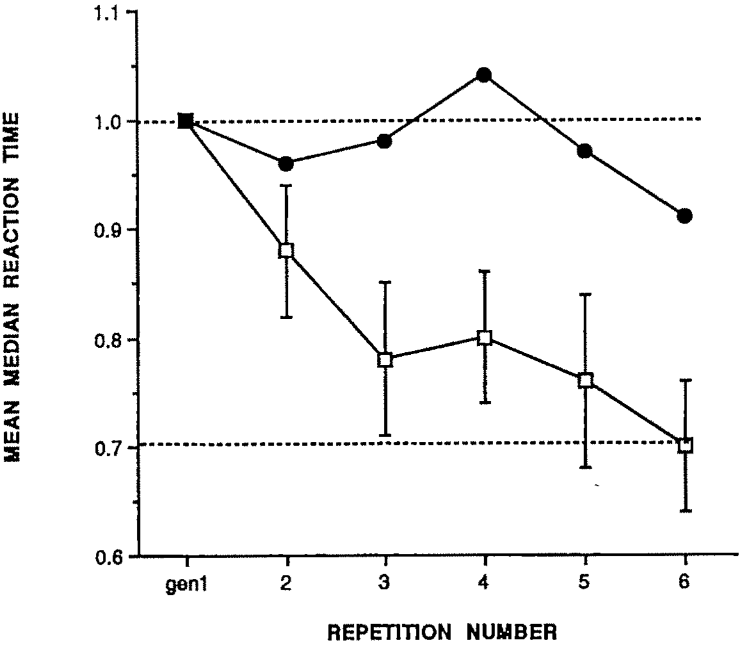

FIG. 2 Reaction times across six repetitions of the verb generation task for RC1 (closed circles) and three controls (open squares). Values are normalized to the mean median reaction time for the first block of the task (gen1) Upper dashed line indicates initial performance, lower dashed line indicates mean performance of the controls on the final repetition Error bars indicate standard error of the mean for controls.

trials, subjects were presented with 20 words, and asked to verbally produce their responses as quickly as possible. The same 20 words were then presented, in a different order, twice more, and subjects were told they were to work at giving their answers as quickly as possible. No words were used across more than one generation task.

Responses on all tasks but the verb generation were assessed by asking five naive raters to evaluate the correctness of all responses. For each task, a scoring sheet was created which consisted of all 20 stimulus words; after each stimulus word all unique responses, in alphabetical order, generated by RC1 and the control subjects across the three blocks of the given task were listed. The instruction for the given generation task was provided at the top of the sheet, and based upon this instruction raters were asked to circle all responses which they felt were incorrect. Total rater error for each block of each generation task was then computed by summing, across raters, all circled responses made by a subject in that block; thus, the maximum total rater error for a given block is 100 (20 responses, each circled as incorrect by the five raters).

The specific generation tasks were as follows. (1) Category generation: 'Each word will be an example of a member of a category; you should try to think of a label for the category represented by the word. For example, if given "colonel" you might say "officer", or for "Columbus" you might say "explorer".' (2) Attribute generation: 'You should think of a characteristic of the word; something the word usually has or possesses. It might be a physical part of the word, or something more abstract. It should be something that "belongs" to the word. For example, if given "rifle" you might say "trigger", or for "continent" you might say "rivers".' (3) Synonym generation: 'You should think of a synonym for each word; a word which means roughly the same thing as the word you see. For example, for "pig" you might say "hog", and for "shove" you might say "push".' (4) Phoneme generation: 'For each word, take the first sound in the word, and give another word that begins with the same first sound, Your answer does not have

TABLE 2 VERBS GENERATED IN RESPONSE TO PRESENTED NOUNS (FIRST 25 RESPONSES PRODUCED IN BLOCK 6)

Presented noun	*Generated response*		
	RC1	*Control (A F.)*	*Most common (%**)*
Tree	Treehouse*	Climb	Climb (64)
Money	Market*	Spend	Spend (48)
Blanket	Warm	Wrap	Cover (47)
Razor	Sharp*	Shave	Shave (58)
Ice	Cool	Freeze*	Melt (27)
Job	Work	Work	Work (77)
Toy	Play	Play	Play (97)
Gun	Hurt*	Shoot	Shoot (97)
Broom	Clean	Sweep	Sweep (94)
Scale	Weigh	Weigh	Weigh (77)
Hose	Fire	Water	Spray (37)
Letter	Read	Write	Write (39)
Foot	Ten*	Scratch*	Walk (40)
Oven	Heat	Heat	Heat (9)
Bed	Sleep	Make	Sleep (72)
Bee	Sting	Spell*	Sting (76)
Lens	See	See	See (47)
Soap	Clean	Wash	Wash (84)
Dog	Cat*	Play	Bark (31)
Plane	Boat*	Fly	Fly (85)
Fist	Ten*	Make	Hit (47)
Brick	Red*	Lay	Throw (43)
Pill	Small*	Take	Take (59)
Pool	Swim	Swim	Swim (100)
Phone	Listen	Call	Call (58)

* = response not generated by any of 35 previous subjects; ** = percentage of responding subjects who generated given answer.

to look like the presented word, have the same meaning, or even start with the same letters (for example, ''c'' and ''k'' sometimes sound alike). Sometimes the initial sound will not be made from a single letter, for example, the ''cl'' sound in ''club''. For example, given the word ''ideal'' you might say ''island'', and for ''club'' you might say ''cluck''.' (5) Verb generation: 'For each word, you should think of an associated verb; something you might do to the word or something it might do. For example, for ''picture'' you might say ''frame'', or for ''hand'' you might say ''grasp''.' A subset of the nouns used in the previous study of verb generation were used as stimuli. Control subjects were not tested on this task, since they were asked to perform the original version of the verb generate task in the same session.

Results. Results are presented in Table 3. RC1's reaction time decreases on the synonym, attribute and category generation tasks were more than three standard deviations above the decreases shown by controls. Once again, RC1's initial performance was within the range of control values for all but one of the generation tasks; for the category generation task, RC1 was initially faster than all three of the controls, though his median reaction time was still within two standard deviations of the mean for controls. When retested on the verb generation task, RC1 showed a median reaction time decrease of 18%, which, though better than his prior improvement on the generate task, was still below the performance of the controls on the synonym, attribute and category generation tasks (decreases for controls ranged from 26% to 49%), The one generation task for which RC1 did show a normal reaction time decrease with learning was the phoneme generation task: RC1's median RT decreased 64%, compared with 77% for the normals (a difference of less than one standard deviation).

RC1 also produced a large number of incorrect answers. For example, when asked to generate a synonym to 'garbage' he responded with 'old', when asked to generate a category label for 'cookie' he responded

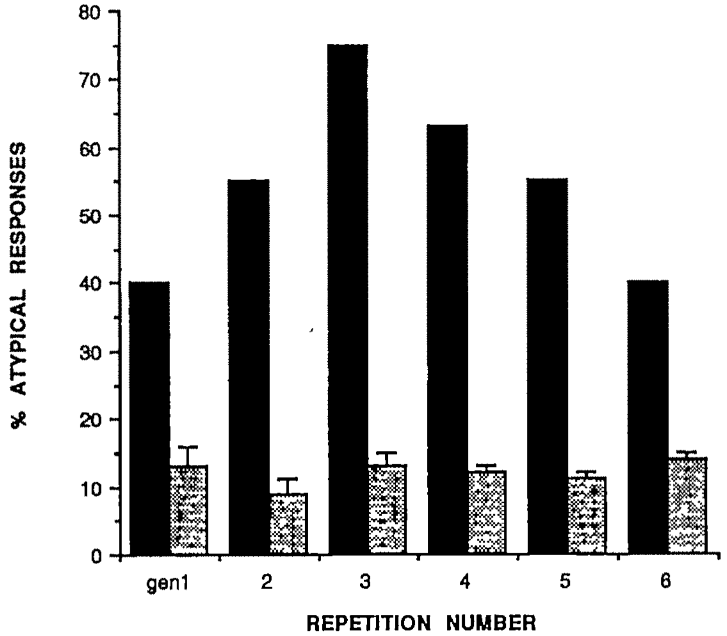

FIG. 3. Percentage of atypical responses across repetitions of the verb generation task for RC1 (filled columns) and three controls (stippled columns). Responses are defined as atypical if none of 35 previous subjects generated the same answer for a given noun. Error bars indicate standard error of the mean for controls.

TABLE 3 INITIAL PERFORMANCE AND LEARNING ACROSS GENERATION TASKS

	Reaction time (ms)				*Learning (block 1/block 3 reaction time)*			
Task:	*Synonym*	*Category*	*Attribute*	*Phoneme*	*Synonym*	*Category*	*Attribute*	*Phoneme*
A.F.	876	1118	1202	1512	0.72	0.63	0.59	0.59
W.A.	1518	1302	2338	3657	0.74	0.72	0.51	0.84
K.A.	1186	1728	1454	1494	0.76	0.53	0.56	0.87
Mean	1193	1383	1664	2221	0.74	0.63	0.55	0.77
SD	321	313	596	1244	0.02	0.10	0.04	0.15
RC1	1236	843	1545	3291	0.91	0.96	0.81	0.64

with 'eat', and when asked to generate an attribute for 'butterfly' he responded with 'insect'. Results from the error analysis are given in Table 4. On none of the blocks for any of the generation tasks was RC1's rater error less than any of the controls. For eight out of 12 blocks, RC1's rater error was more than 2.5 standard deviations above the mean control performance. With the exception of the attribute generation task, RC1 showed no tendency to reduce his errors across blocks; his rater error summed across all of the first blocks of the generate tasks was 87, versus a total of 85 across the third blocks.

RC1's responses on the verb generation task were evaluated using the method described for the initial longer version of the task. 0%, 0% and 10% of his responses were atypical on blocks 1, 2 and 3 of the task, respectively.

Discussion. Taken as a whole, RC1's performance on the various generation tasks suggests he had a general deficit in producing typical and correct responses, as well as an abnormal lack of improvement with practice. RC1's improvement on his second exposure to the generate task, and his normal performance on the phoneme generation task, stand as exceptions to his performance on the other generation tasks.

TABLE 4 RATER ERROR ACROSS BLOCKS OF GENERATION TASKS

Task.	*Synonym*			*Category*			*Attribute*			*Phoneme*		
Block.	*1*	*2*	*3*	*1*	*2*	*3*	*1*	*2*	*3*	*1*	*2*	*3*
A.F	12	9	9	13	14	14	3	3	3	1	1	3
W.A.	10	8	9	6	6	6	12	14	12	8	5	8
K.A.	10	8	7	15	7	9	4	5	3	8	1	5
Mean	11	8	8	11	9	10	6	7	6	6	2	5
SD	1.2	0.6	1.2	7.4	4.4	4.0	4.9	5.6	5.2	4.0	2.3	2.5
RC1	26	24	25	30	30	27	20	18	12	11	5	16

It seems most likely that RC1's low error rate on the short version of verb generation task reflected his extensive exposure to the verb generation task, as well as the nouns used as stimuli, during his initial testing; this exposure included not only performance of the original generate task, but also more informal use of the noun list and task. However, it is possible that his improvement was due to either some recovery from his lesion, or learning of the task which occurred following the initial testing (due to consolidation, etc.).

It is unclear why RC1 showed normal learning of the phoneme task. Two possibilities seem most likely: (1) a fundamental difference exists between the phoneme and other generation tasks (for example, unlike the other tasks, responses for the phoneme task might be generated without reference to a semantic associate); or (2) based upon block 1 reaction time values, the phoneme is the most difficult of the generation tasks; it is possible that for both RC1 and controls, the learning reflects a general, rather than item-specific, improvement on the task, and had more trials been conducted RC1 would have plateaued at a value much higher than the controls. The available data do not allow us to distinguish between these and other possibilities. Investigations in other patients should clarify this issue and yield valuable information about the mechanisms underlying the learning deficits.

Converging studies

RC1's performance on rule-based generation tasks suggested two specific areas in which RC1 was impaired: (1) practice-related learning; (2) error detection. For each of these areas, a set of converging tasks was designed to evaluate more fully the nature and extent of RC1's difficulties.

Learning task: concurrent discrimination learning

Unlike the generation tasks, subjects were not under time pressure, nor did they have to select an answer using semantic and/or syntactic rules. Both word and pattern versions of the task were administered. For the word version, 20 pairs of words were used, and one word in each pair was arbitrarily preassigned to be the positive member. Subjects were told that they were to learn, through trial-and-error, the positive word in each pair; after indicating a selection by pointing, subjects were told whether they were correct or incorrect. The same set of word pairs was then repeated until a subject made no errors on four consecutive blocks, up to a maximum of 20 blocks. In order to prevent subjects from learning a pattern of pointing, pair order and item position were varied across blocks. Members of each pair were matched for frequency, letter and syllable length, and part-of-speech. Subjects proceeded through the cards at their own pace.

For the pattern version of this task the same paradigm was used, except the stimuli consisted of 18 black-and-white pattern pairs repeated across a total of 12 blocks. Both word and pattern pairs were displayed on 4×6 index cards.

Results. Results from the word discrimination learning are shown in Fig. 4. For word discrimination learning, all controls showed a significant negative correlation between percent incorrect responses and block number ($P < 0.01$ for all controls, simple linear regression; for each subject, data from all blocks prior to the third consecutive block with no errors was used for the analysis). The controls also showed a similar correlation for the pattern disscrimination learning ($P < 0.01$ for all controls, simple linear regression; all blocks were used for each control). RC1, however, failed to show significant improvement across blocks for either the word or pattern discrimination learning ($P = 0.97$ and 0.28, simple linear regression). Based upon the regression slopes and intercepts, the mean number of trials required to achieve perfect performance for controls extrapolates to 14 ± 4 for the word discrimination and 17.5 ± 7 for the pattern discrimination, versus 1880 and 46 for RC1.

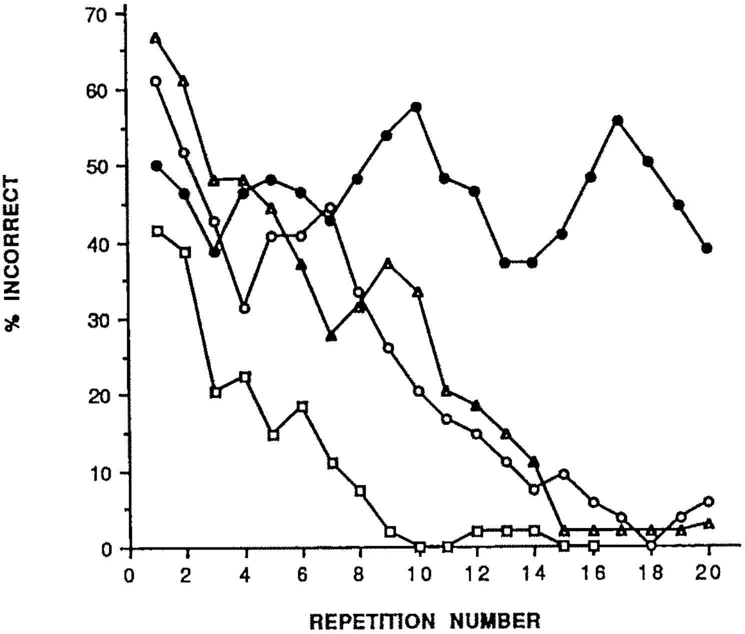

FIG. 4 Percentage of incorrect responses across repetitions of the word concurrent discrimination learning task for RC1 (closed circles) and three controls: A F. (open circles), W A (open squares) and K A (open triangles) Values are smoothed across three repetitions by calculating the mean for each repetition and the preceding (if any) and succeeding (if any) repetitions.

Learning task: Tower of Toronto

The Tower of Toronto puzzle, a simplified version of the Tower of Hanoi, was administered according to the procedures outlined by Saint-Cyr *et al.* (1988), with the exception of allowing an unlimited number of moves to complete the puzzle instead of placing a 50-move maximum. Solutions to this puzzle are similar in concept to those for solving the more complicated Tower of Hanoi: a set of discs, each a different colour, must be moved from a starting to a finishing position by shifting individual discs among three pegs. The only rules are that only one disc can be moved at a time, and a darker coloured disc can never be placed on top of a lighter disc. The testing begins with three practice blocks, in which only three discs are used. Immediately after the practice blocks, subjects are requested to complete the puzzle five times in succession, using four discs. After a 1 h to 1.5 h delay, subjects are again asked to complete the puzzle five more times in succession, again using four discs. With three discs, the puzzle can be completed in a minimum of seven moves, whereas with four discs a minimum of 15 moves is required.

Results. An index score was computed according to a formula outlined in the original methodological description of the puzzle (Saint-Cyr *et al.*, 1988). For the 10 blocks using four discs the following is summed:

index score = (no. of blocks with 17 or less moves+10)−(no. of blocks with 30 or more moves).

A score of less than 9 is considered impaired. RC1's score was 1, four standard deviations below the mean score of 11 for controls. For purposes of comparison, RC1's score is similar to reported values for advanced stage Huntington's disease patients, who show signs of global dementia (Saint-Cyr *et al.*, 1988). RC1 does show improvement on the task. He averaged, for the first five blocks, 52 moves required to complete the puzzle, versus an average of 34 moves required across the last five blocks, a significant decrease ($P < 0.01$, unpaired two-tailed *t* test). RC1's improvement occurred largely across blocks 1−6;

he plateaued at 33 moves required to complete the puzzle, a value higher than the smoothed mean required by controls on any of the 10 blocks and still above the 30-move ceiling for not deducting points from the index score (*see* Fig. 5).

RC1's improvement can be analysed by examining the sequences of moves he made to solve the puzzle across the various blocks. If all of the possible legal moves of the Tower of Toronto puzzle are examined, four 'critical choices' can be isolated. These correspond to nodes along various solution sequences in which a non-optimal choice produces the greatest penalty in terms of the number of moves required to recover from the error. Learning puzzles such as the Tower of Toronto involves not only reducing the number of moves required to complete the puzzle, but also applying the solution principles which allow the 'critical choices' to be made correctly. Learning the solution principles appears to be a skill acquired independently of an ability to verbalize a solution strategy or to consciously recollect previous experience with the puzzle (Cohen *et al.*, 1985). While RC1 reduced the number of moves he required to recover from a non-optimal 'critical choice' across blocks 6–10 (primarily because he 'back-tracked' through the puzzle less frequently), he did not appear to learn the solution principles of the puzzle. On block 9, 3 out of 4 of RC1's 'critical choices' were not-optimal; and on block 10, 4 out of 4 of his 'critical choices' were non-optimal; for both blocks RC1's performance was more than a standard deviation above the control means of 1.3 and 1.0 non-optimal choices on blocks 9 and 10, respectively.

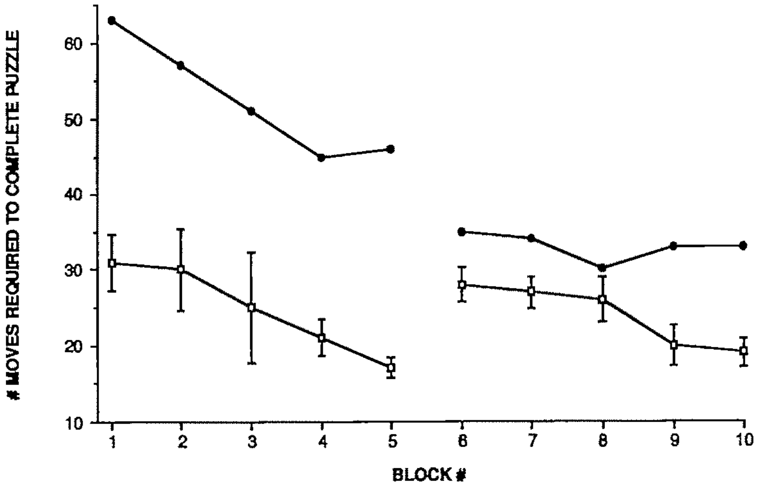

FIG 5, Number of moves required to complete the Tower of Toronto puzzle across 10 blocks for RC1 (closed circles) and three controls (open squares). For all 10 blocks four discs were used, allowing the puzzle to be completed in a minimum of 15 moves. Following the fifth block there was a 1 h to 1.5 h delay. Values are smoothed across three blocks by calculating the mean for each block and the preceding (if any) and succeeding (if any) blocks; blocks 1–5 were smoothed independently of blocks 6–10. Error bars indicate standard error of the mean for controls.

Error detection: recognition of errors

For the most part RC1 did not seem to realize that his responses were abnormal. When initially tested on the verb generation task, for instance, RC1 only once indicated that he had made a mistake: when he violated the instructions to provide a single-word answer by responding to 'chair' with 'four legs', he remarked, 'saying more than one word'. At several times during his initial testing, RC1 was auditorily given nouns he had previously seen and asked to generate verbs for them. In some cases, when he produced an incorrect response, he was reminded that a verb should be an action word telling what the noun might do or what it might be used for, and was provided with an example of an appropriate response to the noun. Under these conditions RC1 still made errors, and only once indicated he had given a non-verb answer ('wire' in response to 'phone'). During subsequent rule-based generation tests he indicated that he thought some of his answers were wrong, but did not explicitly identify any incorrect answers; furthermore, as already discussed, overall he failed to reduce his errors with repeated exposure to the same stimuli.

Error detection: contextual influence

When given stronger constraints for the selection of responses, RC1 made fewer errors. On the day following his initial testing on the verb generation task, RC1 was auditorily presented with 38 of the nouns for which he had generated verbs the previous day. For the first 20 nouns, RC1 was asked once again to produce a verb answer. Immediately following this task, RC1 was asked to respond to the next 18 nouns by replying, 'You (*answer*) with it', or 'It (*answer*)'. The typicality of RC1's responses were classified as previously described, and compared with responses produced on his sixth exposure to the nouns the previous day. For the first 20 nouns, 11 out of 20 of his responses were atypical (accepting atypical verb derivations, such as 'swimming' in response to 'pool' as typical responses), versus 8 out of 20 the previous day. For the next 18 nouns, 1 out of 17 of his responses was atypical ('travel' in response to 'boat'), versus 8 out of 17 in the previous day.

Error detection: timed forced-choice adjective/verb discrimination

For a forced-choice test of verb/adjective discrimination, subjects were presented with individual words that they identified as either adjectives or verbs by pressing one of two response keys. Subjects were told that the adjectives would be description words, whereas the verbs would be action words. Each word remained on the screen until either a key was pressed or 9 s had elapsed since the initial presentation of the word. Following a keypress, the word was erased, and after an intertrial interval of 1.5 s the next word was presented.

Results. When asked to decide whether a presented word was an adjective or a verb as quickly as possible, RC1's median reaction time was 2054 ms, more than four standard deviations above the mean of 919 ms for controls. RC1's accuracy (94% correct) was within a standard deviation of the mean for controls (90% correct).

Error detection: untimed forced-choice category and synonym discrimination

RC1 was given a worksheet containing 40 words, some of which had previously been presented as stimuli during the synonym generation task. Beside each word there were two possible answers, some of which were responses he had made previously to the words during the generation task. Only one answer was listed as a synonym in an on-line computer thesaurus (Word Finder, Microlytics, Inc., Pittsford, NY, USA). All possible answers were associated to the stimulus word; for example, for the word 'wed' the possible choices were 'ring' and 'marry', and for the word 'beautiful' the choices were 'glamorous' and 'gorgeous'. He was asked to circle the 'best' synonym for each word. He was told that some of the answers would be close in meaning, and that he should think carefully before making his decision. He was told to take as much time as he wanted to complete the worksheet. Due to an oversight, controls were given a slightly different worksheet, in which the choices for the word 'tall' were 'lanky' and 'high', rather than 'lanky' and 'skyscraper', and one of the stimulus words and associated possible answers was different. A similar worksheet was created also containing 40 words, some of which had previously been presented as stimuli during the category generation task. Once again, possible answers were both associated for a given stimulus word, and some choices were those he had made previously to words during the category generation task. Subjects were told to circle the best category label for each word (e.g. circle 'colour' rather than 'golden' in response to the word 'yellow'). Both RC1 and controls were given the same category worksheet.

Results. In calculating errors, only those stimulus words and associated possible answers which were common to both versions of the synonym worksheet were considered. RC1 made five errors, over three standard deviations above the control mean of 0.7 errors. RC1's errors were all made when asked to select from two closely associated words, e.g. 'unearth' and 'explore' as alternative answers for 'discover'. On the forced-choice category worksheet RC1 made no errors, less than a standard deviation below the mean of 0.7 errors for controls.

Specific dissociations

Delayed non-matching to sample

RC1 may have been unable to distinguish between or remember stimuli used for the word and pattern discrimination learning tasks. As a test of this possibility he was given both word and pattern versions of a delayed non-match to sample task.

Method. A trial consisted of a single word or pattern stimulus displayed in the centre of a sample card for approximately 3 s. The card was then removed from sight. After a 5 s, 15 s or 60 s delay period, a test card was shown containing a novel stimulus and the previously presented sample stimulus. RC1 was asked to point to the novel stimulus. The delay lengths were pseudo-randomly mixed, as was the position of the novel stimulus on the display card.

For the word version of this task, words were printed in bold-faced lower-case letters and taped to a 4×6 inch index card. The sample and novel stimuli words used in each trial were matched for frequency, letter and syllable length, and part-of-speech. Five trials with a delay of 5 s, eleven trials with a 15-s delay, and nine trials with a 60-s delay were given.

For the pattern version of this task, black-and-white patterns were taped to a 4×6 inch index card. Eight trials with a delay of 5 s, 15 trials with a delay of 15 s and 15 trials with a delay of 60 s were given.

Results. RC1 made no errors on either the word (25 out of 25 correct) or pattern (35 out of 35 correct) versions of this test. Control subjects were not tested on either version of the task.

Stroop colour/word interference

It is possible that RC1 knew that his answers were incorrect, but was unable to prevent himself normally from responding with stronger associates to the presented rule than those which match the rule for response generation. In order to determine whether RC1 had a global inability to inhibit pre-potent responses, he was asked to perform a Stroop colour/word interference task, a task in which subjects are provided with strong conflicting information which must be ignored in order to produce a correct response (Stroop, 1935).

Method. For the first block (the incongruent colour block), each stimulus was one of three colour names ('red', 'blue' or 'green') displayed in an incongruent colour (red, blue or green). Subjects were asked to name the display colour as quickly as possible. For the second block (the congruent colour block), a string of Xs was displayed in either red, blue or green, and subjects were again asked to name the display colour as quickly as possible. For the third block (the congruent word block), one of three colour names ('red', 'blue' or 'green') was displayed in black, and subjects were asked to read the colour name as quickly as possible. Only two control subjects were given this task, because the third control subject was colour-blind.

Results. Across all blocks, RC1's median naming time was greater than that of the two tested controls: 760 ms (RC1) versus 702 ms and 702 ms (controls) for the incongruent colour block; 584 ms (RC1) versus 543 ms and 560 ms (controls) for the congruent ink block; and 560 ms (RC1) versus 509 ms and 451 ms (controls) for the congruent colour block. For all three subjects, an incongruity ratio was calculated by dividing the reaction time for the incongruent colour block by the average reaction time value for the two congruent blocks:

$$\text{incongruity ratio} = \text{incongruent colours}/((\text{congruent words}+\text{congruent colours})/2).$$

RC1's incongruity ratio was 1.33 versus 1.33 and 1.39 for the two controls, indicating the degree of interference caused by conflicting information was the same for both RC1 and controls, despite RC1's slower naming times.

Lexical decision

As mentioned in the analysis of RC1's generation task errors and reaction times, his median response time across all generation tasks was not significantly different from controls, despite the fact that his simple naming time was slower for nouns and stimuli used for the Stroop task. This raises the possibility that RC1 had a global speed/accuracy trade-off abnormality. A lexical decision task was administered as a test of this hypothesis.

Methods. Subjects were presented with letter strings that they identified as either real words or pronounceable non-words by pressing one of two response keys. Each letter string remained on the screen until either a key was pressed or 9 s had elapsed since the initial presentation of the letter string. Following a keypress, the letter string was erased, and following an intertrial interval of 1.5 s the next letter string was presented.

Results. RC1's speed and accuracy on the lexical decision task were 702 ms and 96% correct. The mean values for controls were 655 ms and 98% correct, both of which are within a standard deviation of RC1's values.

Summary

RC1 failed to successfully complete and normally learn the verb generation task. His performance on this, and other generation tasks, was characterized by the production of associated but incorrect answers according to the rule given for response generation. Even when placed in two-alternative forced-choice situations, RC1 still performed below controls. RC1 also failed, unlike controls, to decrease his reaction time with practice on a given set of words. This learning deficit, initially noted as a failure to improve with practice on the generate task, extended to a variety of other tasks, such as word and pattern concurrent discrimination learning.

In contrast to his deficits, RC1's scores of all administered standard neuropsychological tests, including those of intelligence, language, 'frontal function' and memory, were at or above normal. He also performed similarly to controls on specific tasks designed to measure delayed recall and control of response production (both the ability to inhibit a pre-potent response and maintain a normal speed/accuracy trade-off criterion).

DISCUSSION

Attributing causality to the cerebellar damage

A concern with any single-case study must be the extent to which the results may be due to an individual peculiarity, pre-existing impairment or undetected neurological damage. RC1's above-average to superior performance on standard intelligence, memory and language tests makes it difficult to account for his disorders on the basis of a global dysfunction; these tests are sensitive measures of even early stages of senile dementia (Storandt *et al.*, 1984; Adams *et al.*, 1986; O'Donnell *et al.*, 1988). Furthermore, it is unlikely that RC1's deficits can be explained on the basis of task difficulty: even Huntington's disease patients with clear signs of dementia achieve higher scores on the simple Tower of Toronto task than RC1 (Saint-Cyr *et al.*, 1988). Finally, in three independent readings, radiologists failed to note any evidence in RC1's MRI and CT scans for cortical damage, including excessive cerebral atrophy, infarcts, haemorrhages or other non-specific damage.

It is possible that RC1's cerebral metabolism was affected by his cerebellar damage. Secondarily reduced cerebellar metabolism ('crossed cerebellar diaschisis') has been correlated with frontal cortical damage in approximately half of patients examined (Pantano *et al.*, 1986; Baron, 1989); though not as well characterized, similar changes in the contralateral frontal cortex ('reverse cerebellar diaschisis') have been correlated with cerebellar damage in some patients (Broich *et al.*, 1987; Anderson *et al.*, 1988). Functional deficits have been associated with secondary hypometabolism; in general, the hypometabolism and associated deficits have been interpreted as a loss of functional input to the secondary region, rather than a dysfunction of the region (Deuel and Collins, 1984; Powers and Raichle, 1985; Perani *et al.*, 1987; Metter *et al.*, 1989); however, the relationship between secondary metabolic changes and functional deficits is an active area of research, and much remains to be answered. It is reasonable to question whether RC1's deficits might be accounted for by a purely secondary regional dysfunction.

Some aspects of RC1's performance might suggest some frontal impairment resulting from his cerebellar damage. However, despite RC1's impairments on some language tasks, and his production of errors, he showed no evidence of a 'frontal lobe syndrome'. He was not impaired on standard tests of language difficult for frontal aphasics to perform (Goodglass and Kaplan, 1983), and his word fluency was normal, a language deficit commonly found even in non-aphasic frontal patients (Benton, 1968; Perret, 1974; Miller, 1984). Frontal patients tend to produce responses which are contextually inappropriate, reverting to the production of 'habitual' responses (Luria, 1966, 1980; Stuss and Benson, 1986). Though not systematically investigated, case reports suggest that some frontal patients make errors despite their knowledge that their response is incorrect (Luria, 1980; Konow and Pribram, 1970; Picton *et al.*, 1986); RC1, on the other hand, did not appear to recognize his errors. Furthermore, he was able to inhibit strong habitual responses on the Stroop task, and made only six errors on the Wisconsin Card Sorting Test; both of these tasks are difficult for frontal patients to perform, because of difficulty in maintaining a cognitive 'set' and a tendency for response perseveration (Milner, 1963; Drewe, 1974; Perret, 1974; Robinson *et al.*, 1980). On the Picture Arrangement subtest of the WAIS, a task which appears to be sensitive to difficulties in temporal sequencing and planning associated with frontal damage (Medina *et al.*, 1954; Logue *et al.*, 1968; Hamlin, 1970), RC1's score was perfect. Finally, no changes in RC1's personality were reported by his wife, contrary to common reports that frontal patients tend to lack drive, self-motivation and inhibition of socially-inappropriate behaviour (Penfield and Evans, 1935; Grafman *et al.*, 1986; Stuss and Benson, 1986).

The relationship between the cerebrum and cerebellum

Based upon present theories regarding secondary hypometabolism, and the pattern of deficits seen in RC1, it is most reasonable to conclude that his deficits were more closely associated with his primary cerebellar damage than with a secondary frontal or other cortical dysfunction. This is not to argue, however, that deficits common to patients with cerebral damage and patients with cerebellar damage cannot be identified. In fact, evidence already exists which suggests prism adaptation might be impaired following either frontal or cerebellar damage (Weiner *et al.*, 1983; Canavan *et al.*, 1990), and performance on a task similar to the Tower of Toronto appears impaired following frontal damage (Shallice, 1982). These results do not mean that the processing required for successful performance on these tasks is solely dependent upon the frontal cortex. Rather, it suggests that for particular tasks there is a strong functional relationship between the cerebellum and the frontal cortex; presumably, each region performs a particular type of processing which may be important for successful task performance, and loss of either one may produce impairments. In other words, mental operations appear to be localized, but performance of a complex task requires an integrated ensemble of brain regions (*see* Damasio and Damasio, 1990, and Posner *et al.*, 1988 for a discussion of this theory). For instance, in addition to the right cerebellum, a number of frontal cortical regions are activated when normal subjects produce verb associates to visually presented nouns, and these regions are activated by different components of the task (Petersen *et al.*, 1989).

How the cerebellum and the cerebral cortex might interact for successful task performance is a complex question beyond the scope of the present report (*see* Leiner *et al.*, 1991 for a discussion of this topic). The purpose of the present study was to examine what particular processing deficits might be associated with damage to the cerebellum. The remainder of the discussion will focus on how RC1's learning and error detection deficits can be understood in light of known motor functions of the cerebellum, and the implications the results may have for mechanisms of memory and learning. Substantiation of the hypotheses developed regarding RC1's deficits, and a more complete ability to place them in the context of deficits associated with damage to other brain regions, will clearly require further investigation, involving cerebellar as well as other patient populations (such as those with frontal or medial temporal cortical damage).

The cerebellum and error detection

RC1 produced a large number of inappropriate responses across a variety of rule-based generation tasks. These errors were particularly striking because they contrasted so markedly with his extremely fluent and grammatically correct conversational skills, as well as his normal performance on standard measures of language function. It is possible that RC1's errors were caused by an inability to control his output. However, RC1's normal performance on tasks which require inhibition of a pre-potent response and establishment of a normal speed/accuracy trade-off criterion argue against this explanation. Furthermore, if RC1's errors resulted from a problem with response control, it seems most likely that he would have been aware of his errors. When RC1 responded once with a multi-word answer, he did comment that he had made a mistake; this suggests RC1 was capable of evaluating at least some type of errors after they had been made. On the other hand, during formal testing RC1 never explicitly identified any of his semantic/syntactic errors. Taken as a whole, the evidence suggests RC1's errors resulted from a diminished ability, on a trial-by-trial basis, to successfully evaluate the correctness of his responses, both before and after their production.

RC1 not only produced errors, but he also had difficulty perceiving errors: when asked in a two-alternative forced-choice test to select synonyms from non-synonyms, his performance was impaired. This suggests RC1's errors reflected a general impairment in both perception and production processes which require the detection of errors in at least some high-order analyses, including tasks requiring particular semantic/syntactic processing of linguistic information. Investigations of timing functions of the cerebellum have similarly led to a proposed role of the cerebellum in both timing production and timing perception (Ivry and Keele, 1989).

RC1's deficits in error detection are consistent with evidence that the cerebellum carries information regarding a variety of motor errors, and that this information can be used to make corrective adjustments to ongoing motor behaviour. This is well demonstrated by the vestibular-ocular reflex (VOR) and smooth-pursuit systems. The VOR helps stabilize visual images on the retina by producing compensatory eye movements in response to vestibular input caused by head movement. When an imperfect compensatory eye-movement occurs, the result is a displacement of an image on the retina (retinal slip) (Miles and Lisberger, 1981; Ito, 1982). In monkeys, some of the same neural machinery is used for accurate tracking of moving visual objects (Miles and Lisberger, 1981). Based upon Purkinje cell discharges in the cerebellar flocculus, it appears that climbing fibres carry information about retinal slip; furthermore, this climbing fibre discharge may be specifically related to retinal slip which needs to be corrected, and not to other occurrences of retinal slip (such as occur when monkeys are required to fixate and avoid tracking a moving target). Analysis of the known VOR and smooth-pursuit circuitry suggests climbing fibre discharges alter Purkinje cell output, which helps compensate for VOR and smooth-pursuit errors (Stone and Lisberger, 1990).

Though the details are less complete, in other systems climbing fibres also seem to carry information about errors which result in corrective cerebellar ouptut. Studies of cat and ferret locomotion have shown elevated climbing fibre discharges when the step cycle is unexpectedly perturbed (Lou and Bloedel, 1986; Andersson and Armstrong, 1987). In tasks requiring reaching to a spatial target, or movement of a manipulandum to a target zone, perturbations can be caused by changing the manipulandum load to the target. For these tasks also, climbing fibre discharge has been correlated with the perturbation (Gilbert and Thach, 1977; Wang *et al.*, 1987).

In summary, RC1's deficits and physiological recordings made during the performance of various motor tasks suggest that information about ongoing performance which signals a performance error is conveyed to the cerebellum, typically via climbing fibres. As a result, cerebellar output is modified, which in turn produces corrective motor output. In this sense, the cerebellum may act as a central interface between a sensory representation which in some environmental contexts may signal an error, and the motor response to a performance error.

The cerebellum and learning

Marr (1969), in an elegant theoretical demonstration based upon the architecture of the cerebellum, proposed that the cerebellum was a modifiable pattern recognition system which could be used to develop motor skills. Marr's cerebellar learning model was followed shortly by a similar model detailed by Albus (1971). Lesion and physiological studies have since provided compelling evidence to support the involvement of the cerebellum in learning and suggest that climbing fibres serve an important instructive function in the learning process. The role of the cerebellum in motor plasticity has been most extensively investigated in studies of the VOR. Though normally the reflex is extremely precise, performance can be disrupted by requiring subjects (monkeys, cats or humans) to wear magnifying or reducing prisms. Over time, the system adapts to the vestibular-visual gain changes produced by the prisms, and performance returns to initial levels (Jones, 1977; Miles and Eighmy, 1980). Plasticity of the system is lost, or severely reduced, following lesions of the cerebellar flocculus in rabbits and monkeys (Ito *et al.*, 1974; Lisberger *et al.*, 1984). Other types of motor plasticity are also affected following cerebellar damage. For example, performance in a manipulandum task which requires a precise motor output against a known load is disrupted by substitution of a novel load. Adaptation to such load changes is disrupted by cerebellar lesions in humans and monkeys (Gilbert and Thach, 1977; Keating and Thach, 1990). In both of these cases, climbing fibre discharge has been correlated with the learning process: in the early stages of learning, climbing fibre discharge is high, and after appropriate adaptation has been achieved, climbing fibre discharge declines to initiate levels (Gilbert and Thach, 1977; Watanabe, 1984).

Associative learning is also affected by cerebellar lesions. Eye-blinks in rabbits can be classically conditioned by pairing a conditioned stimulus (e.g. a tone or light flash) with an unconditioned stimulus (e.g an air puff). Following training, the motor response to an unconditioned stimulus (an unconditioned response) is also produced in response to the conditioned stimulus (a conditioned response) (Gormezano *et al.*, 1962). Lesions of the interpositus nucleus appear to abolish both reaquisition and retention of a conditioned response, while the unconditioned response appears largely intact (Yeo *et al.*, 1985; Lavond *et al.*, 1990; but *see* Welsh and Harvey, 1989). Cerebellar cortical lesions disrupt, but do not abolish, reacquisition of the conditioned response (Lavond and Steinmetz, 1989; Harvey *et al.*, 1990). Based upon evidence from both lesion and electrical stimulation studies, it appears that climbing fibres carry information about the unconditioned stimulus, while mossy fibres carry information about the conditioned stimulus (Yeo *et al.*, 1986; Lewis *et al.*, 1987; Steinmetz *et al.*, 1989). Initially, climbing fibre discharge is correlated with the presence of the unconditioned stimulus, but as the conditioned response is learned the discharge declines (Thompson, 1986).

Finally, the cerbellum appears to be involved in a variety of other types of conditioning, as well as some types of habituation. For example, the cerebellar vermis appears to be essential for both classically-conditioned bradycardia in rats (Supple and Leaton, 1990), and long-term habituation of the acoustic startle response (Leaton and Supple, 1986). Cerebellar lesions also disrupt conditioned leg flexion in dogs and discrimination conditioning (e.g. respond to a sphere but not a triangle) in both dogs and fish (reviewed by Karamian *et al.*, 1969).

Despite above-average memory abilities, RC1 failed to learn normally a variety of tasks. Those tasks in which RC1 was impaired share similarities to motor tasks also affected by cerebellar lesions. The verb generation task can be thought of in some sense as requiring plasticity in a motor response. It may be that an important aspect of learning this task is the modification of the most typical but incorrect response to the presented word (either the name of the word or its strongest associate) so that the strongest associate becomes an appropriate verb. The concurrent discrimination task requires the subject to associate, through trial and error, one of two stimuli with a verbal reward. The task is similar to those types of motor conditioning shown to be affected by cerebellar lesions. For all of those tasks which appear to involve the cerebellum, practice results in the development of consistent responses to repeated stimuli. Mishkin and Petri (1984) have theorized that the learning which results automatically from experience with a stimulus-response relationship is distinct from a memory, and might be more accurately termed a 'habit'.

One critical question is the extent to which RC1's errors and failure to exhibit normal learning on the various generation tasks reflect dysfunction of a single underlying process. One possibility is that the process of detecting an error cannot be separated from that of correction and learning. Such an interpretation is consistent with PET evidence that cerebellar activation during performance of the verb generation task occurs in naive subjects who only performed the task once (Petersen *et al.*, 1989), and that reaction times decreased for control subjects upon second exposure to the list of nouns, even though they were unaware that the task would be repeated. Further supporting a possible link between error correction and learning is evidence that, for the VOR and visual/motor arm tasks, error information is used to correct for perturbations in an ongoing motor behaviour, and is correlated with adaptation to a consistent change caused by prisms or load changes. However, in none of these systems has a causal relationship between error information and learning been demonstrated.

Consistency within the learning and memory literature

Not only are RC1's learning and error-detection impairments consistent with postulated motor functions of the cerebellum, but they are also consistent with a growing body of data which suggests the existence of at least two different long-term memory systems. Studies of humans with severe amnesia caused by medial temporal and midline diencephalic damage have shown amnesics are severely impaired on memory tasks which appear to rely heavily upon conscious recall of previous experience (e.g. *see* Corkin, 1984; Squire, 1986). On the other hand, it has been shown that amnesics normally benefit from previous experience on some tasks. For instance, amnesics show normal improvement on a variety of skill learning tasks, such as mirror tracing (e.g. Cohen *et al.*, 1985; Squire, 1986; Knopman and Nissen, 1987). Amnesics also tend to show normal priming effects, i.e. the biasing of future responses or alteration of response times due to previous exposure to a particular stimulus (reviewed by Schacter, 1987). In general, the pattern of deficits found in humans has been replicated in monkey models of amnesia (e.g. *see* Aggleton and Mishkin, 1983; Zola-Morgan and Squire, 1984, 1985).

RC1, in many respects, appears to possess a pattern of deficits opposite to those found in human amnesics. Whereas typical scores for amnesics on the Wechsler Memory Scale are 79.3 (Aggleton *et al.*, 1988), 77.4 (Squire *et al.*, 1988), and 67 (Corkin, 1984), RC1's score of 124 is above average and comparable with his score on the WAIS-R evaluation of intelligence. RC1's delayed recall subscore was 121. Similarly, on both pattern and word versions of a delayed non-match to sample task, RC1 made no errors, while similar studies in monkey and human amnesics have reported greater than 25% errors following only a 30 s delay (Zola-Morgan and Squire, 1985; Squire *et al.*, 1988; Overman *et al.*, 1990).

Conversely, RC1 was dramatically impaired on the Tower of Toronto task. Even populations with severe memory deficits, as measured by the WMS-R, appear to learn this task normally (Saint-Cyr *et al.*, 1988). Furthermore, there is some evidence that the more complicated Tower of Hanoi can also be learned by amnesics (Cohen *et al.*, 1985). Though amnesics have not been asked to perform the verb generation task, the absence of a significant hippocampal activation during performance of the task suggests it does not make important contributions to the learning of the task (Petersen *et al.*, 1989).

Finally, studies with monkeys indicate that the hippocampus and amygdala may not be necessary for normal concurrent discrimination learning (Phillips *et al.*, 1988; Overman *et al.*, 1990). Given RC1's deficit on this task, normal learning may depend upon activation of a cerebellar learning circuit. However, a number of investigators have failed to replicate normal concurrent discrimination learning in human amnesics (Oscar-Berman and Zola-Morgan, 1980; Aggleton *et al.*, 1988; Squire *et al.*, 1988). Several interpretations exist for this discrepancy, including: (1) in humans, both the cerebellum and the hippocampus may be important for normal performance, which would suggest that use of the two structures is not necessarily mutually exclusive; (2) the human amnesics may have confounding cerebellar damage. The memory impairment studies have typically resulted from Wernicke-Korsakoff's syndrome, senile dementia of the Alzheimer type, or medial temporal resections used to treat intractable epilepsy. For all three etiologies, cerebellar as well as hippocampal and/or midline diencephalic damage may occur. Typical motor signs of cerebellar dysfunction occur in the Wernicke's phase of the Korsakoff syndrome, and in many cases it is likely that permanent cerebellar damage results (reviewed by Butters, 1984). Chronic alcohol abuse by itself also appears to result in cerebellar atrophy (Meigaard and Ahlgren, 1986; Harper and Kril, 1990). Recently, several investigators have reported that amyloid plaques in the cerebellum may not be as rare as initially thought (Cole *et al.*, 1989; Wisniewski *et al.*, 1989). Finally, cerebellar atrophy is not uncommon in severe epileptics; it is unclear whether this typically results from seizure activity or the long-term effects of anti-epileptic medication (Salcman *et al.*, 1978; Botez *et al.*, 1988).

Summary

The pattern of deficits observed in RC1 provide a foundation for further investigations into non-motor functions of the cerebellum and the functional relationship between the cerebral cortex and the cerebellum. RC1 failed to learn and perform normally a variety of tasks which involve complex non-motor ('cognitive') cortical processing. It seems most probable that RC1's deficits were caused by his loss of important cerebellar contributions to the performance on certain types of both motor and cognitive tasks, particularly those involving the development and modification of consistent responses to repeated stimuli. Based upon the differential pattern of deficits between RC1 and amnesics, the contributions made by the cerebellum to learning and memory appear, for at least some tasks, to be dissociable from the contributions made by medial temporal and midline diencephalic structures. This suggests the cerebellum may be a critical part of one of at least two anatomically distinct long-term human memory/learning systems.

We feel our investigations of RC1's deficits demonstrate the utility of using information from PET studies of normal human performance to guide lesion-behaviour studies. Combining information across these two techniques can be particularly valuable when, as occurred in the case of the cerebellar activation, the PET finding cannot be readily accounted for on the basis of existing data. In such instances, beginning a neuropsychological investigation with a task known to produce activation of a lesioned area may provide novel information about the processing performed by the lesioned area during the chosen task.

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POSTURAL DISTURBANCES DUE TO HOMONYMOUS HEMIANOPIC VISUAL ATAXIA

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SUMMARY

Patients with visual defects often complain of disturbances of equilibrium. In order to measure the influence of visual stimulation on posture, a study was made comparing the posture of hemianopic patients with that of healthy volunteers before and after occlusion of half of the monocular visual field. Hemianopia increases lateral oscillations in patients in the standing position and the projection of the body's centre of gravity shifts towards the hemianopia: in the volunteers, the same shift is noted after masking half the visual field. A tonic effect of visual information is discussed.

INTRODUCTION

Postural control is achieved through a multisensory process to which proprioceptive information from the mechanoreceptors of the joints and the muscles of the legs, and information of vestibular and visual origin contribute. Recently, the importance of visual patterns for postural control and for the equilibrium of the body in space has been demonstrated (Dichgans *et al.*, 1976; Paulus *et al.*, 1984). In fact, Kleint (1936) suspected the pre-eminent role of vision in postural control and Gibson (1958) concluded that the flow pattern of an optic array provides feedback stimulation for the control and guidance of locomotor behaviour which he referred to as 'visual kinesthesis'.

Lee and Aronson (1974), studying the stimulatory effects on children of a moving room, came to the same conclusion, i.e. that visual proprioception is a pre-eminent factor in determining stance. Closing the eyes increases the oscillations of the body in a vertical position. Edwards (1946), Witkin and Wapner (1950) and Hashiba *et al.* (1981) have measured these oscillations with the aid of a platform and shown that 'the visual information from the peripheral field is more effective in body stabilization than from the central visual field'. In confirmation of these results obtained from man, Mirka and Brookhart (1981) have shown in canine postural control that only the peripheral field produced visual feedback that affected postural control.

Clinical observations suggest that very often patients with homonymous hemianopia complain of disturbances of equilibrium. Since experimental results have shown the importance of vision and in particular of peripheral vision in postural control, we have made a study of the posture of patients with visual field defects.

PATIENTS

Thirty-three patients and 56 healthy volunteers having given their informed consent were carefully examined by a neurologist. All patients had a computerized tomographic examination and an examination

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of vision including the visual fields using a Goldman perimeter and visual acuity. Patients were selected who had no evidence of cerebellar, labyrinthine or proprioceptive ataxia. Muscular strength and all other modalities of sensation were normal in all patients. None had vestibular disturbances on clinical examination and 16 patients subjected to detailed vestibular investigation (caloric testing and electronystagmography) showed no abnormality. Unilateral spatial or motor neglect was not observed in any patient. Subjects and patients were divided into six groups. Further clinical data are summarized in Tables 1A,B,C.

Group I. Forty-six normal subjects, 23 men and 23 women (mean age 53 yrs).

Group II. Twelve patients with right homonymous field defects.

Group III. Fifteen patients with left homonymous field defects.

Group IV. Ten normal subjects (mean age 57 yrs), five men and five women, with the right half of the right molecular visual field occluded with visual field masks.

Group V. Ten normal subjects (mean age 57 yrs), five men and five women, with the left half of the left monocular visual field occluded.

Group VI. Six brain damaged patients, without visual abnormalities, selected according to the above criteria and specially screened to exclude any motor or proprioceptive defect. These patients had anterior brain lesions

TABLE 1 CLINICAL FEATURES

Case	*Sex*	*Patient's age at time of recording*	*Age of lesion at recording*	*Etiology*	*Site of lesion*	*Neurological disorder*
A. Group II	Right campimetric defects					
1	F	47	7 yrs	Haematoma	O	–
2	F	79	2 mths	PCA isch.	O	–
3	M	43	1 mth	PCA isch.	TO	Constructional apraxia+alexia
4	F	56	5 mths	Traumatism	?	Left oculomotor nerve palsy
5	F	64	Several yrs	Meningioma	PO	–
6	M	22	22 yrs	Porencephalia	TP	–
7	F	71	6 mths	PCA isch.	O	Constructional apraxia
8	M	23	23 yrs	Choroid plexus papilloma	PO	–
9	F	79	4 yrs	PCA isch.	PO	Visual hallucinations
10	M	41	6 mths	Unique metastasis	PO	Visuo-motor apraxia Inf. Quad
11	M	47	8 yrs	Haematoma	TP	Visuo-motor apraxia Sup. Quad.
12	M	50	5 mths	PVA isch.	O	Visuo-motor apraxia Sup Quad

Mean age = 52; the visual acuity was normal except case 4: left blind eye. Patient 2 with bilateral Parkinson's disease was treated for several years before the visual defect. Patient 9 had bilateral posterior cerebral ischaemia

B. Group III: Left campimetric defects						
13	F	73	1.5 yrs	PCA isch.	O	Constructional apraxia
14	F	91	4 yrs	PCA isch	O	–
15	F	57	10 mths	PCA isch.	O	–
16	M	72	1 mth	Haematoma	PO	Constructional apraxia
17	M	80	2 yrs	PCA isch.	O	Constructional apraxia Prosopagnosia—loss of topographical memory
18	M	49	4 mths	PCA isch.	P	Constructional apraxia
19	F	79	2 yrs	PCA isch.	TO	Transitory loss of topographical memory Inf. Quad.
20	M	73	6 yrs	Haematoma	O	Transitory loss of topographical memory Inf Quad.

Case	*Sex*	*Patient's age at time of recording*	*Age of lesion at recording*	*Etiology*	*Site of lesion*	*Neurological disorder*
21	M	58	1 yr	PCA isch.	O	Transitory loss of topographical memory Inf. Quad.
22	M	60	1 mth	PCA isch.	PO	Constructional apraxia Inf. Quad
23	M	46	1 mth	PCA isch.	TO	Constructional apraxia Inf Quad
24	M	72	1 mth	PCA isch.	PO	Transitory loss of topographical memory Inf. Quad.
25	M	63	3 yrs	PCA isch.	O	Loss of topographical memory Sup. Quad.
26	M	46	1 mth	PCA isch.	TO	Mild constructional apraxia Sup. Quad.
27	F	70	5 mths	Glioma	PTO	Loss of topographical memory Prosopagnosia—Constructional apraxia Sup. Quad.

Mean age = 67. The visual acuity is normal except in patient 16 (1/10° at each eye) Some had neuropsychological disorders but none of them had unilateral spatial agnosia

C. Group VI Brain damage without visual defect

Case	*Sex*	*Patient's age at time of recording*	*Age of lesion at recording*	*Etiology*	*Site of lesion*	*Neurological disorder*
28	M	19	2 yrs	Isch.	Right lecticular nucleus	Left superior pyramidal syndrome
29	M	31	1 mth	Isch.	Left premotor area	–
30	F	54	1 yr	Isch	Left premotor area	Right pyramidal syndrome without motor deficit
31	M	41	4 yrs	Oligo-dendro glioma	Left lecticular nucleus + frontal area	–
32	M	66	4 yrs	Haematoma	Right internal capsule	Left superior pyramidal syndrome
33	M	60	1 mth	Lacune	Left internal capsule	Right pyramidal syndrome without motor weakness

O = occipital; P = parietal, T = temporal; PCA = posterior cerebral artery, Inf = inferior, Sup. = superior; Quad. = quadrantanopia; isch = ischaemia.

METHODS

Measurement of body sway

The subjects stood on a force moment measuring platform (Rottembourg, 1976). The platform was supported at each of its corners by electromagnetic force transducers which measured locally three orthogonal forces (antero-posterior, lateral and vertical). By adding up the outputs of these four transducers in charge amplifiers the three components of the subjects' reaction forces on the platform and the reaction moment about the lateral and antero-posterior axes were obtained.

The displacement of the resultant centre of force was calculated from these force components. The displacement of the resultant centre of force is equivalent to the displacement of the centre of gravity only at very low frequencies and this was available for our study. At higher frequencies dynamic components due to body inertia add to the static forces and account for less than 10% of 0.2 Hz (Gurfinkel, 1973).

Data recording

The subjects stood on the platform with heels 2 cm apart and feet splayed at an angle of 30 degrees. They were instructed to stand as straight as possible and refrain from any voluntary movement during the three recording trials for 20 s. Each recording, with eyes open in daylight and eyes closed, was separated by a period of 15 min. The subjects looked at a white vertical line 5 m away which was aligned exactly along the middle of the platform, and the stationary visual environment in the near periphery of the visual field was provided by 3 m of featureless white wall as described in Gagey (1980). The measurement was discarded if the preset position of the feet had changed or if any disturbance had occurred during the recording

Data analysis

The equipment consisted of a Tektronix 700 oscilloscope, a numeric table and a digital computer (PDP 11). The signal received on the oscilloscope was transformed in real time by a chopper and an analogue to digital converter. We used a low pass second order filter and the sampling rate of body sway measurements was 102 Hz.

Calculation of sway parameters

Posture recordings were available in a linear mode and in vectographic modes. The linear mode refers to the linear development of the projection of the subject's centre of gravity onto his sustaining polygon. The linear plot shows the dissociation between antero-posterior Hy and lateral Hx sways. The length of the curve which has no conventional unit of measurement was calculated according to the following equation:

$$l = \sum_{t=1}^{511} \sqrt{(Hx_t - Hx_t - 1)^2 + (Hy_t - Hy_t - 1)^2}.$$

In vectography, the length of the curve, traced by the centre of force in a 20 s period, is referred to as the sway path and was calculated using the same equation. The envelope of the sway path was evaluated and assimulated to an area according to the method described by Takagi (1983). From this area we derived the percentage of the antero-posterior and lateral sways.

RESULTS

The results are given successively in terms of the linear development of the shifts of the centre of force, then in terms of the area describing the envelope of the sway path and finally in terms of postural laterality, expressed in arbitrary units (positive on the right).

Length of curve (*eyes open and eyes closed*) (Table 2, Fig. 1)

Group I (normal range). In normal subjects no antero-posterior component was larger than the lateral. With eyes open the ratio of the antero-posterior/lateral curve lengths was 4/3. With eyes closed, a non-significant increase of all oscillations was observed.

Groups II and III (right and left field defects). With eyes open and all the line lengths, antero-posterior, lateral and sway path were increased 1.5-fold. Comparison of groups I and II, and I and III showed a significant difference (Fig. 1). The antero-posterior lengths were always larger than the lateral ones, as in normal subjects (Fig. 1). With closed eyes, the oscillations decreased. The difference between test runs with eyes open and eyes closed was significant for group II ($P < 0.05$, lateral component and sway path), and for group III ($P < 0.001$).

Groups IV and V (masking of either the right or the left half of the monocular visual field). With eyes open, all line lengths (antero-posterior, lateral and sway path) were increased 1.5-fold as in groups II and III, and the antero-posterior lengths were consistently greater than the lateral ones, as in group I (Fig. 1). With eyes closed, the oscillations were the same.

TABLE 2 LENGTH OF CURVE

		AP		*Lateral*		*Sway path*	
		OE	*CE*	*OE*	*CE*	*OE*	*CE*
Group I	Mean	133	140	92	98	178	183
	SEM	5.6	5.6	3.1	3.2	3.9	3
Group II	Mean	164	165	125*	117	223*	212
	SEM	12.9	14.8	9.6	10.3	16.9	19.5
Group III	Mean	192***	171	137***	122	255***	222
	SEM	14.9	14.2	11.3	12.5	20.2	15.2
Group IV	Mean	158	160	114	115	207	210
	SEM	10.4	11.3	8.4	8.7	12.8	14.7
Group V	Mean	157	138	125	126	217	234
	SEM	10.5	12.2	11.1	11.1	13.8	16.3
Group VI	Mean	138*	145	97**	102	180***	188
	SEM	5.7	5.9	3.3	3.3	4.1	3.4

AP = antero-posterior component; *OE* = eyes open; *CE* = eyes closed; SEM = standard error mean; $^{*}P = 0.05$; $^{**}0.002 < P < 0.05$; $^{***}P < 0.002$. (*P* refers to the difference between OE and CE conditions.)

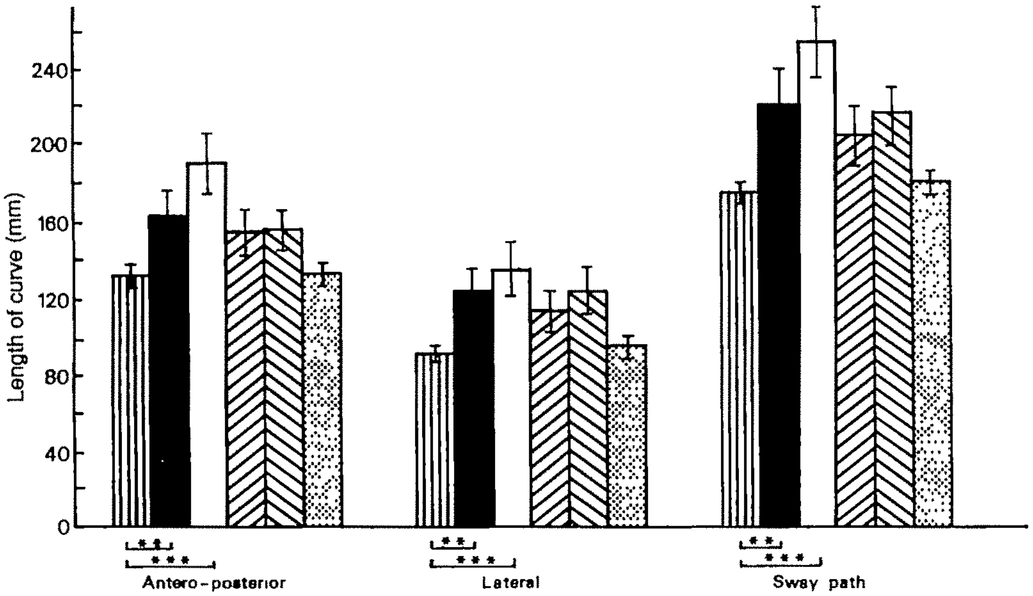

FIG 1. Length of the curve (mm), eyes open (the error bars represent SEM); ▥ = normal range (group I), ■ = right field defects (group II); ☐ left field defects (group III); ▨ = experimental right field defects (group IV); ▩ = experimental left field defects (group V), ░ = brain-damaged patients without visual defects (group VI)

Group VI. With eyes open, all the lengths were within normal limits. There were no significant differences between groups I and VI.

Area (eyes open and eyes closed) (Table 3, Fig. 2)

Group I (normal range). With eyes open the ratio of the antero-posterior to the lateral areas was 2.33. With eyes closed the increase in oscillations was not significant.

TABLE 3 AREA UNDER THE CURVE AND POSTURAL LATERALITY

		AP		*Lateral*		*Sway path*		*Postural laterality*
		OE	*CE*	*OE*	*CE*	*OE*	*CE*	*OE*
Group I	Mean	21	21	9	13	8 1	13.2	8
	SEM	2.2	2.2	2 3	2.4	0.8	0.9	–
Group II	Mean	30.2**	28.5	31 7**	28	43.5	40 3	16.2
	SEM	3.1	3	3.2	2.8	7.15	5.8	–
Group III	Mean	30.2***	25	39.8**	31.4	61.7***	51 6	−15.5
	SEM	2.8	1.8	3 9	3.2	9.5	7 5	–
Group IV	Mean	28.1	28.4	29.4	30.4	41.4	42 1	14.8
	SEM	3 0	3.0	2.9	3.1	7.1	6 2	–
Group V	Mean	27.4	28.3	40.4	39.3	56.4	62.5	−8.1
	SEM	29	2 4	3.7	3.7	8.4	9.5	–
Group VI	Mean	18.8**	22.9	23.5*	25.5	19 7**	20.4	7.1
	SEM	2.4	2.4	3	3.3	1.7	1.7	–

AP = antero-posterior component, *OE* = eyes open; *CE* = eyes closed, SEM = standard error mean; *$P = 0.05$, **0 002 $< P < 0.05$; ***$P < 0.002$. (P refers to the difference between OE and CE conditions.)

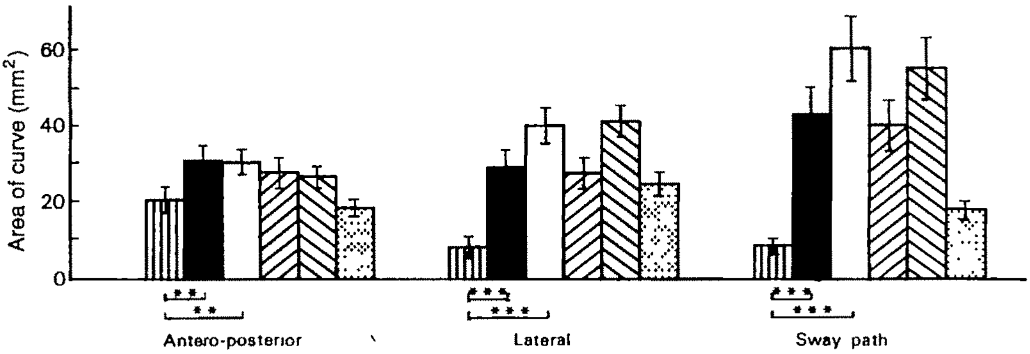

FIG. 2 Area under the curve (mm²), eyes open, ▥ = normal range (group I), ■ = right field defects (group II), □ = left field defects (group III); ▨ = experimental right field defects (group IV), ▧ = experimental left field defects (group V), ░ = brain damaged patients without visual defects (group VI).

Groups II and III (right and left field defects). With eyes open, for group II, the lateral displacement increased and reached the same level as the antero-posterior displacement. For group III, the antero-posterior/lateral ratio was inverted (3/4). The lateral displacement increased sufficiently to reverse the ratio observed in the normal subjects (Fig. 2). With eyes closed, the oscillations decreased. For the antero-posterior component, there was a significant difference between groups I and II and groups I and III. This difference was even more significant ($P < 0.001$) for the lateral component (Fig. 2). The differences of the lengths and the areas between the test runs with eyes open and eyes closed were significant for group II ($P < 0.02$) and for group III ($P < 0.01$).

Groups IV and V (masking of either the right or the left half of the monocular visual field). With eyes open, the lateral displacement of groups II and IV fitted exactly that of groups III and V. With eyes closed, the oscillations were the same as with open eyes.

Group VI. With eyes open, the antero-posterior component lay within the normal range; the lateral component, and the sway path were increased threefold. With eyes closed the oscillations increased in the same proportion as group•I.

Postural laterality (eyes open and eyes closed) (Fig. 3)

Group I (patients in the normal range). The projection of the centre of gravity was to the right (+8) of the theoretical mid-line (Fig. 3).

Group II (patients with the right field defects). The projection of the centre of gravity of the mean of the subjects was +16.2 to the right of group I's projection.

Group III (patients with left field defects). The projection of the centre of gravity of the subjects was averaged at −15.5, to the left of the normal range's projection, but also to the left of the theoretical mid-line.

Group IV (subjects with experimental right field defects). The projection of the centre of gravity of the mean of the subjects was +14.8 to the right of groups I's projection.

Group V (subjects with experimental left field defects). The projection of the centre of gravity of the subjects averaged −8.1 to the left of the normal range's projection, but also to the left of the theoretical mid-line.

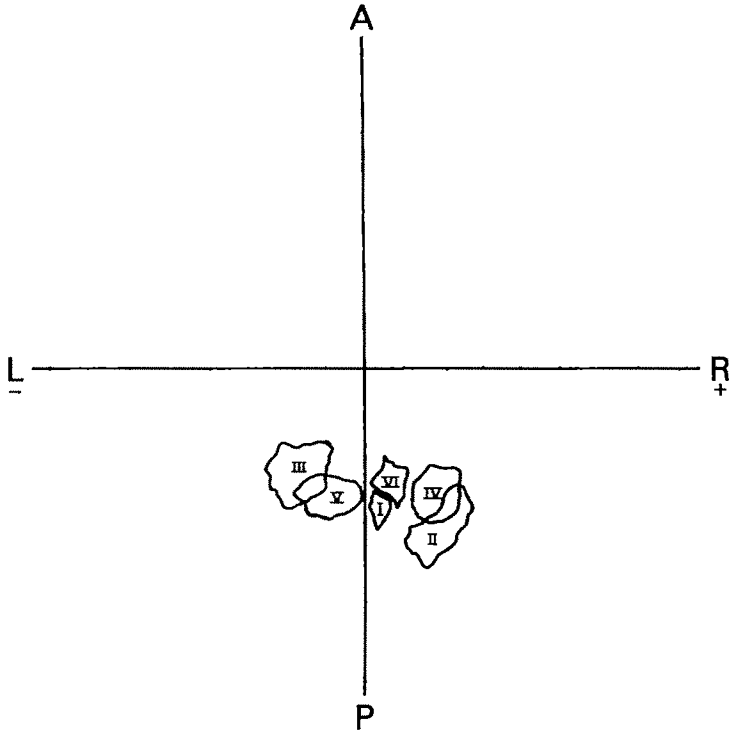

FIG. 3 Posture and homonymous hemianopia Analogue representation of the projection of the gravity centre of the mean of the subjects for the different groups. I and VI = no visual field defect, II and IV = right visual field defect; III and V = left visual field defect; A = anterior; P = posterior; L = left; R = right.

Group VI (control). The projection of the centre of gravity of the subjects averaged +7.1, (within the normal range).

The influence of several factors was investigated. In order to examine the possible effects of foveal vision, we compared the results of patients with normal foveal vision (macular sparing) with those of patients without foveal vision. There was no significant difference between a group of 10 patients with macula sparing and a group of six patients without foveal vision. The extent of the visual defects was also examined: of the 27 patients, 15 were hemianopic and 12 quadrantanopic. We compared the lengths and areas of groups II and III: there was no statistical difference between hemianopic and quadrantanopic groups. Only for group III was there less deviation of the centre of gravity from the theoretical mid-line for quadrantanopic (−1) than for hemianopic (−15) patients. Unfortunately, the numbers were too small to compare upper and lower quadrantanopia.

Comments

The posturographic records confirm the clinical observation that patients with field defects have a disturbance of posture consisting of an increase of body oscillation and a change of position of the centre of force, the direction of which depends on whether the hemianopia is right or left.

In fact, body sway was significantly greater for patients suffering from hemianopia (groups II and III) and for volunteers with experimental field defects (groups IV and V) than for the two control groups I and VI. There was an increase of lateral oscillations: the oscillations in the normal range occurred along an antero-posterior axis, while in the hemianopic group they occurred more along a lateral axis. There was a significant increase in the lateral component and sway path area in groups II and III compared with those in group I; also in groups IV and V compared with those in group I; but not between group VI and group I (Fig. 2). In the right field defects group, the lateral oscillations were equal to the antero-posterior. In the group having left field defects, the lateral oscillations were greater than the antero-posterior. These results are the same for groups II and III (right and left field defects) as for group IV and V (experimental right and left field defects). For postural laterality, the projection of the centre of gravity was usually to the right of the theoretical mid-line in normal subjects, more to the right for the right field defects group and to the left for the left field defects group. Therefore, the direction of body displacement was always to the side of the hemianopia. Postural laterality was the same for groups I and VI (Fig. 3). Thus, it appears that a deficiency of peripheral vision is of prime importance in determining postural disturbances (Hashiba *et al.*, 1981). To evaluate the compensation of these defects with the passage of time, we compared two groups of patients with field defects of different duration. For the seven patients with hemianopia of less than 3 mths the mean area of the sway path envelope was 60, whereas for the six patients with hemianopia lasting from 1 to 3 yrs before examination, the mean area of the sway path envelope was 41 and for the four patients suffering from hemianopia for more than 7 yrs, the mean area of the sway path envelope was only 34. These results indicate that there is potential for compensation, albeit limited: after 7 yrs, the mean area of the sway path envelope was still 34 compared with 8.1 for the control group.

DISCUSSION

The instability of which patients with field visual defects complain is due to postural disturbance which is clearly shown by posturographic records. We have suggested calling it 'Visual Ataxia' (Valade *et al.*, 1983). Patients who have brain damage without hemianopia do not show a modification of postural laterality so that brain damage without hemianopia does not provoke such ataxia. The ataxia indicates the importance of visual input in postural control and particularly of peripheral input: the postural instability was identical whether or not foveal vision was preserved or not. Our conclusions confirm those of Paulus *et al.* (1984) on this point: 'inclusion or exclusion of the fovea itself inside a larger stimulus field leads to almost no differential effect', as well as the experimental findings of Mirka and Brookhart (1981) and the conclusions of Hashiba *et al.* (1981).

As to the mechanism of this postural disturbance, the ataxia did not seem to be of labyrinthine origin: caloric and electronystagmorgraphic examination results were normal. On the Fast Fourier Transform, we did not observe the peak at 0.30 Hz described in vestibular affections (Dichgans *et al.*, 1976). Moreover, it would be odd for vestibular impairment always to be localized to the same side as the hemianopia. The subjects with experimental right or left visual defects showed the same deviation as patients with homonymous field defects.

Another explanation could be a recentring of the body in relation to the spared visual field: if patients are not able to see in their masked half of the visual field, there might be a tendency to orientate the body axis in the spared visual field, leading to a permanent modification of posture. But in this case, the abnormal axis would be in the middle of the remaining visual field, with a deviation of the body on the normal side. We observed an opposite deviation. Unilateral spatial neglect could be considered a determining factor. It is particularly observed in right hemisphere lesions (Brain, 1941). We did, in fact, observe that postural disturbances were especially important in group III; but patients with left hemispheric lesions also suffered from postural instability. None of the patients had unilateral neglect or spatial agnosia. Even if they had subclinical spatial neglect, we would have expected them to be able to move on the other side. Heilman *et al.* (1983) undertook a pointing test on a sagittal plane related to the body axis: patients with left spatial neglect showed a right deviation. By contrast, we observed a strong left deviation of the centre of gravity in the left hemianopia group. It seems inappropriate to relate postural deviation to unilateral spatial neglect.

Our results enable us to advance the hypothesis that vision has a tonic influence on posture in each visual hemifield. Normally a state of equilibrium and a vertical posture result from it. If one of the visual hemifields is no longer stimulated, the other one will exercise a tonic effect on posture, tending to displace the body axis to the opposite side, i.e. on the side of the hemianopia. In tests with eyes closed, we observed a shift in the axis of the centre of gravity of the body in hemianopic patients with a decrease in oscillations.

Whatever the nature of the postural effect responsible for ataxia in hemianopic patients, it is certain that visual input plays a prominent part in the regulation of posture. In the case of hemianopia, this equilibrium is upset and the body tends to shift to the side of the hemianopia. The postural defect is further linked to visual disturbances and increases the hemianopic patient's handicap, resulting in a tendency to collide with objects on the visually deficient side.

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SENSORY ABNORMALITIES AND DYSAESTHESIAS IN THE ANTERIOR SPINAL ARTERY SYNDROME

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SUMMARY

We present three patients with a nontraumatic cervical anterior spinal artery syndrome, two of whom developed painful burning dysaesthesias below the level of spinal cord lesion, refractory to opiate, anticonvulsant and tricyclic antidepressant therapy. Quantitative sensory testing and neurophysiological assessment showed absence of pain and temperature sensation below the level of the lesion, with preservation of light touch, vibratory and position sensibilities and cortical somatosensory evoked potentials in all three patients. Dysaesthesias in both affected patients were exacerbated by somatosensory input attributed to intact posterior column function. Posterior column electrical stimulation worsened the dysaesthesias in one affected patient, and was ineffective in the other. Both patients affected with dysaesthesias showed significant improvement in motor function and developed clinical spasticity, while the third patient developed neither dysaesthesias nor spasticity, but remained flaccid without motor improvement, suggesting a more complete lesion of anterolateral spinal pathways. These cases illustrate that lesions of the anterolateral spinal cord may lead to the development of dysaesthesias, perhaps related in part to selective neospinothalamic deafferentation and preservation of the posterior columns.

INTRODUCTION

The anterior spinal artery syndrome (ASAS) is an anterior myelopathy with multiple potential etiologies (Spiller, 1909; Grinker and Guy, 1927; Zeitlin and Lichtenstein, 1936; Steegmann, 1952; Paine and Byers, 1953; Hughes and Brownell, 1964; Lyon, 1971; Foo and Rossier, 1983; Mody *et al.*, 1988). The syndrome is characterized by the acute onset of leg weakness, sphincter disturbance and a dissociated sensory loss below the level of spinal cord lesion; pain perception and temperature discrimination are impaired while vibratory and position sense remain intact. Weakness of the arms may be present depending on the level of spinal cord involvement. The prognosis for recovery in ASAS is poor, but varies with the etiology of the syndrome and the degree of sensory and motor impairment. Although improvement occurs in a substantial proportion of cases (Foo and Rossier, 1983) little attention has been focused on pain (Tasker and Dostrovsky, 1989) or dysaesthesia (Pagni, 1989) as sequelae of this syndrome.

Central pain refers to pain occurring in association with central nervous system (CNS) lesions (Riddoch, 1938). Such pain may occur spontaneously, and is often evoked with innocuous stimulation. Central pain has been associated with sensory loss since the original description of thalamic pain by Dejerine and Roussy (1906). Clinical evidence suggests that the propensity to develop central pain is independent of the level within the neuraxis

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at which central afferent pathways are damaged (Riddoch, 1938; Pagni, 1977, 1989; Tasker and Dostrovsky, 1989). Thus, central pain syndromes may complicate stroke (Dejerine and Roussy, 1906; Riddoch, 1938; Pagni, 1977, 1989; Boivie *et al.*, 1989; Leijon *et al.*, 1989; Tasker and Dostrovsky, 1989) as well as spinal cord injury (Riddoch, 1938; Pollock *et al.*, 1951; Davis, 1975; Pagni, 1977, 1989; Davidoff *et al.*, 1987; Berić *et al.*, 1988; Tasker and Dostrovsky, 1989).

The identification of potential pathophysiological mechanisms for the genesis of spontaneous pain associated with CNS injury has been hindered by the fact that pathological lesions usually affect multiple contiguous structures (Pagni, 1977). In contrast, therapeutic surgical procedures often result in highly selective lesioning of individual sensory pathways. Careful analysis of the outcome from a variety of these surgical interventions has shown that central pain is most likely to develop after interruption of the spinothalamic tract (Pagni, 1977, 1989; Nathan and Smith, 1984; Tasker and Dostrovsky, 1989). Recent clinical studies of post-stroke pain (Boivie *et al.*, 1989; Leijon *et al.*, 1989) and of dysaesthesias following traumatic spinal cord injury (Berić *et al.*, 1988) have confirmed this association physiologically. We now present and compare three cases of nontraumatic cervical ASAS, two of whom developed dysaesthetic pain syndromes below the level of spinal cord lesion. We suggest that these cases strengthen the association (Berić *et al.*, 1988) between the development of dysaesthesias and selective destruction of anterolateral spinal pathways with preservation of posterior columns.

METHODS

From 1985 to 1989, three patients with a clinical diagnosis of anterior spinal artery syndrome were evaluated by the Division of Restorative Neurology and Human Neurobiology.

All three patients received neurological evaluation and a pain interview. This interview included having each patient illustrate and rate pain intensity using a pain drawing and visual analogue scale. Sensory function was evaluated using quantitative sensory testing and somatosensory evoked potentials.

Light touch perception was tested using Von Frey hairs; threshold was recorded as the lowest stimulus intensity detected by the patient on more than 50% of trials. Vibration threshold was determined over the clavicle, second metacarpal, first metatarsal and the anterior surface of the tibia with a vibrameter (Somedic AB) using the method of Goldberg and Lindblom (1979). Thermal sensibility was assessed over cervical, thoracic, lumbar and sacral dermatomes with a thermal stimulator (Somedic AB) according to the method of Fruhstorfer *et al.* (1976).

Median somatosensory evoked potentials (SEPs) were recorded with stimulation of the median nerve at the wrist using Beckman surface electrodes placed over the ipsilateral Erb's point and the C_7 spinous process referenced to the suprasternal notch, and silver-silver chloride cup electrodes placed 1.5 cm posterior to C_3' and C_4' and referenced to F_z as well as to linked ears (international EEG 10/20 system). Tibial SEPs were recorded with stimulation of the tibial nerve at the knee using silver-silver chloride cup electrodes placed 1.5 cm posterior to C_z and referenced to F_z. EKG gating was used for recording evoked potentials with an analysis time of 120 ms as described previously (Berić, 1989).

Nerve conduction studies using standard techniques of percutaneous supramaximal nerve stimulation and surface electrode recording were performed on two patients. Electromyography (EMG) was performed using standard concentric needle electrode technique.

CLINICAL HISTORIES

Patient 1

A 43-yr-old man developed an ASAS with a cervical spinal level following a four vessel cerebral angiogram performed to evaluate a grade I subarachnoid haemorrhage. The results of angiography were inconclusive.

Initial evaluation showed a flaccid quadriparesis with absent pin-prick and temperature discrimination below C_4 and bowel and bladder incontinence. Light touch, vibratory and position sense were normal. During the next 4 mths, motor improvement in his legs was accompanied by the development of marked spasticity, while his arms atrophied and remained flaccid and immobile. The patient complained bitterly of dysaesthesias 6 mths after the onset of ASAS. These were described as continuous 'burning-stinging' and 'burning-aching' sensations radiating from the shoulders down through the legs (Fig. 1). These sensations were exacerbated by light touch, and seemed to be precipitated by lower extremity muscle spasms, impairing attempted ambulation. Intrathecal morphine was administered 7 mths after the onset of ASAS at another institution without affecting the dysaesthesias. Magnetic resonance imaging (MRI) of the cervical spinal cord was normal 8 mths after development of ASAS Carbamazepine, phenytoin and narcotics provided no relief. A spinal epidural stimulator (Neuromed) was placed 12 mths after onset of ASAS, and was initially effective in relieving dysaesthesias However, the patient developed intolerance to epidural stimulation over 2 mths and refused to use the stimulator, claiming it now worsened his dysaesthesias. The stimulator was removed at the patient's request. Five years after onset of neurological deficit he continues to complain of dysaesthesias unrelieved by carbamazepine and amitriptyline.

Patient 2

This 30-yr-old man developed an ASAS following four vessel cerebral angiography. The procedure was performed to evaluate a small area of haemorrhage in the left pons identified with computerized tomography (CT) after the patient developed transient paraesthesias of the right face and body. Past medical history included a traumatic cervical spine fracture at C_2 sustained 2 yrs previously without associated neurological deficit. When first examined, the patient had a flaccid quadriparesis with extensor plantar responses. Examination of the cranial nerves was normal. He had bowel and bladder incontinence and absent pin-prick and temperature discrimination below T_4. Light touch, vibratory and position sense were normal. Magnetic resonance imaging confirmed the small area of haemorrhage in the left pons seen on CT, but also revealed an area of increased T_2-weighted signal in the right cerebellar hemisphere interpreted as infarction. During the next 4 mths, motor improvement and spasticity in the legs were accompanied by atrophy of arm muscles. Dysaesthesias began 8 mths after the onset of neurological deficit. The patient described these as continuous, extremely unpleasant 'burning' and 'electric' sensations radiating from the waist down, and an unpleasant 'tingling' sensation in his hands. The dysaesthesias were exacerbated by touching the affected areas, and interfered with physical therapy. Magnetic resonance imaging of the cervical spinal cord was normal at this time. Nerve conduction studies and EMG showed low amplitude compound muscle action potentials in the arms and evidence of severe axonal degeneration in C_5-T_1 innervated

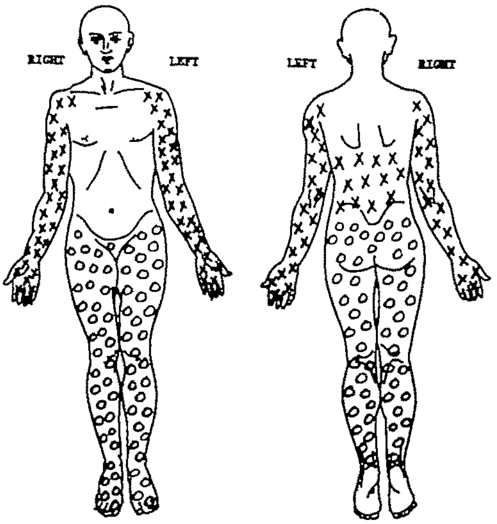

FIG. 1. Pain drawing from a patient with central dysaesthesias and anterior spinal artery syndrome (patient 1). Note the distribution of sensations described as 'burning-stinging' X and 'burning-aching' O.

muscles. Electromyography of leg muscles showed only decreased motor unit recruitment, consistent with an upper motor neuron lesion. Sensory nerve action potentials were normal. Amitriptyline, phenytoin and carbamazepine were administered for 4 mths each without relief from the dysaesthesias. Intrathecal lidocaine produced anaesthesia below a T_{10} spinal level without altering the character of the dysaesthesias An epidural spinal cord stimulator (Neuromed) was implanted at 18 mths after the onset of ASAS, but had no effect on the dysaesthesias. At 30 mths this patient continues to complain of burning dysaesthesias unrelieved by carbamazepine and amitriptyline.

Patient 3

A 25-yr-old woman developed chest pain and fatigue during a vigorous tennis match. Following a brief nap, she was unable to stand. Initial examination showed a flaccid quadriparesis with loss of pin-prick and temperature discriminating below C_5 on the right and below T_6 on the left, with normal light touch, vibratory and position sense. She had bowel and bladder incontinence. Magnetic resonance imaging was consistent with infarction of the cervical spinal cord extending from C_4 to T_1. Nerve conduction studies performed 3 wks after the onset of neurological symptoms showed low amplitude compound muscle action potentials and normal sensory nerve action potentials. Electromyography showed evidence of severe active axonal degeneration in C_5-T_1 innervated hand and arm mucles. Electromyography of leg muscles showed no evidence of denervation. The patient regained some functional use of the right arm during the next 6 mths, while the left arm and both legs remained flaccid and immobile. Neither spasticity nor dysaesthesias had developed by 18 mths after the onset of neurological deficit.

RESULTS

Clinical summary

The clinical characteristics of the three cases of ASAS are summarized in Table 1. Each of our patients developed an anterior thoracocervical myelopathy as evidenced by weakness and atrophy of the arms in association with lower extremity paresis and bowel and bladder incontinence. Clinical evaluation showed that each patient had retention of urine. Clinical status remained virtually unchanged after the onset of neurological deficit in patient 3, while both patients 1 and 2 developed marked spasticity affecting the lower extremities in association with modest motor improvement. Subsequently,

TABLE 1 CLINICAL FEATURES OF PATIENTS WITH ANTERIOR SPINAL ARTERY SYNDROME

Case	*Age (yrs)*	*Sex*	*Etiology*	*Spinal cord level*	*Spastic paraplegia*	*Sphincter disturbance*	*Dysaesthesias below level of lesion*	*Recovery*
1	43	M	Vertebral angiography subarachnoid haemorrhage	C_4	Yes	Yes	6 mths after injury failed DPH, CBZ, AMT and intrathecal morphine, worse with epidural stimulation	Yes Ambulation with spastic gait
2	30	M	Vertebral angiography brainstem haemorrhage*	C_5	Yes	Yes	8 mths after injury failed DPH, CBZ, AMT, intrathecal block and epidural stimulation	Yes Ambulation with spastic gait
3	25	F	Heavy exercise?	C_5	No (flaccid paralysis)	Yes	None by 18 mths of clinical follow-up	None (flaccid paralysis)

*History of asymptomatic C_2 fracture 2 yrs previously DPH = diphenylhydantoin, CBZ = carbamazepine; AMT = amitryptiline.

both of these patients developed functionally limiting dysaesthesias below the level of spinal cord dysfunction.

Quantitative sensory assessment

The sensory profiles of our patients using both quantitative and clinical sensory testing are shown in Table 2. All three patients had absent thermal discrimination and thermal pain perception below the level of spinal cord dysfunction. Pin-prick sensibility was likewise impaired below the level of injury. In contrast, quantitative evaluation of light touch with Von Frey hairs and of vibratory threshold with vibrametry showed that these sensory modalities were relatively unimpaired. Clinical evaluation of graphaesthesia and position sense yielded similar results. The vibratory threshold measured at the first metatarsal in patient 2 was greater than three standard deviations above the mean for this patient's age group; however, this examination was severely limited by spasms evoked during the test. Graphaesthesia was slightly impaired in the lower extremities of patients 2 and 3.

Evoked potentials

Somatosensory evoked potential latencies are shown in Table 3. Median nerve stimulation produced normal evoked responses over Erb's point in each case, while cervical spinal cord evoked responses (N_{13}) were uniformly absent. Cortically recorded evoked potential latencies following median nerve (N_{20}) and tibial nerve (P_{30}) stimulation were normal in patients 1 and 3, and were mildly prolonged in patient 2.

DISCUSSION

We have presented three patients with the anterior spinal artery syndrome. Two of our patients developed miserable dysaesthesias refractory to numerous pharmacological interventions, including oral opiates in both patients and intrathecal morphine in patient 1. All three of our patients had absent thermal discrimination, thermal pain perception and absent pin-prick sensibility below the level of the injury, consistent with an anterior spinal cord lesion, with loss of nociception from the dermatomes affected by the dysaesthesias. Cervically recorded spinal cord evoked potentials (N_{13}) were absent with median nerve stimulation, suggesting dysfunction of the cervical dorsal horn (Restuccia and Mauguière, 1991). However, cortical SEPs with median and tibial nerve stimulation were present in each case, indicating functional integrity of the posterior columns. Preservation of cortically recorded SEPs in a pathologically proven case of ASAS has been observed (Zornow *et al.*, 1990). A previous study in patients with spinal cord injury correlated the presence of SEPs with preservation of sensory perception of vibration and light touch, but not pain and temperature (Berić *et al.*, 1987). Quantitative and clinical sensory testing in all our patients demonstrated sparing of tactile and mechanoreceptive sensory modalities attributed to posterior column function (Nathan *et al.*, 1986; Nathan, 1990); light touch, vibration and position sense were normal in each case.

Tasker and Dostrovsky (1989) state that dysaesthetic pain is usually the result of impaired sensory perception. Physiological impairment of the neospinothalamic tract is demonstrable using quantitative sensory testing in patients with central pain syndromes

TABLE 2. QUANTITATIVE AND CLINICAL SENSORY TESTING IN ANTERIOR SPINAL ARTERY SYNDROME

Patient	*Temperature discrimination*	*Thermal pain perception*	*Pin-prick sensation*	*Light touch Von Frey hairs*	*Vibratory perception*	*Graphaesthesia*	*Position sense*
1	Absent below C_4	Absent below C_4	Absent below C_4	Finger 0.031 N/mm^2 Foot 0.495 N/mm^2	Normal	Normal	Normal
2	Absent below T_4	Absent below C_4	Absent below C_{10}	Finger 0.031 N/mm^2 Foot 0.495 N/mm^2	Slight increase** over feet	Slight decrease over feet	Normal
3	Absent below C_5R/T_6L*	Absent below C_5R/T_6L*	Absent below C_5R/T_6L*	Finger 0.031 N/mm^2 Foot 0 189 N/mm^2	Normal	Slight decrease over feet	Normal
Normal controls	Discrimination of 20–40°C	Heat absent ≤ 50°C Cold absent ≥ 5°C	NQ	Finger ≤ 0.495 N/mm^2 Foot ≤ 1.3 N/mm^2	$\leq$Threshold +2 SD	NQ	NQ

*Results are not lateralized unless specified. **Testing impaired due to evoked spasms. L = left; R = right, NQ = not quantitated but evaluated clinically; SD = standard deviation; N/mm^2 = Newtons per square millimetre.

TABLE 3 SOMATOSENSORY EVOKED POTENTIAL LATENCIES IN ANTERIOR SPINAL ARTERY SYNDROME

		Recording				*Recording*
Patient	*Stimulation*	*Erb's point*	*Spine C_7 (N_{13})*	*Scalp $C'_{3/4}$ (N_{20})*	*Stimulation*	*Scalp C_z-F_z (P_{30})*
1	L median	9.1 ms	NR	19.6 ms	L tibial	32.8 ms
	R median	9.5 ms	NR	20.2 ms	R tibial	33.4 ms
2	L median	9.3 ms	NR	22.0 ms	L tibial	39.6 ms
	R median	9.7 ms	NR	22.8 ms	R tibial	40.0 ms
3	L median	8.3 ms	NR	16.1 ms	L tibial	28.5 ms
	R median	8.3 ms	NR	16.1 ms	R tibial	31.2 ms
Normal	mean ± SD	9.7 ± 0.4 ms	13.0 ± 0.5 ms	18.3 ± 1.2 ms		32.3 ± 1.7 ms

ms = milliseconds, L = left; R = right; NR = no response, SD = standard deviation.

following stroke (Boivie *et al.*, 1989; Leijon *et al.*, 1989) and in patients with dysaesthesias following spinal cord injury (Berić *et al.*, 1988). Dysaesthetic, burning-stinging pain not infrequently accompanies neospinothalamic dysfunction in the lateral medullary syndrome (Currier *et al.*, 1961; Pagni, 1989; Tasker and Dostrovsky, 1989). Further, dysaesthetic central pain frequently follows mesencephalic tractotomy (Drake and McKenzie, 1953), and may complicate anterolateral cordotomy (White and Sweet, 1969; Pagni, 1977, 1989; Nathan and Smith, 1979, 1984; Tasker and Dostrovsky, 1989), possibly as a result of selective surgical lesioning of the neospinothalamic tract (Nathan and Smith, 1984). Posterior column function is preserved in the majority of these patients (Berić *et al.*, 1988; Mauguière and Desmedt, 1988; Boivie *et al.*, 1989; Leijon *et al.*, 1989), as in the present cases of ASAS. The posterior columns also appear to be preserved in macaque monkeys with a deafferentation dysaesthesia syndrome following anterolateral cordotomy (Levitt, 1983). It seems reasonable to ask whether preservation of posterior column function in such cases of central pain and dysaesthesia is causal or merely coincidental.

Berić *et al.* (1988) have suggested that misinterpretation of residual posterior column sensory input in the setting of spinothalamic dysfunction may serve as a mechanism for the genesis of dysaesthesias within the CNS. In this light, it is of some interest that gentle touching of partially deafferented dermatomes evoked dysaesthesias in both of our affected ASAS patients, such somatic stimulation presumably being mediated via intact posterior columns. Indeed, extremely unpleasant over-reaction to sensory stimulation is one of the hallmarks of central pain syndromes (Riddoch, 1938; Pagni, 1989). Dysaesthesias in such patients are frequently evoked by somatic stimuli (Garcin, 1968; Pagni, 1989), as occurred in 85% of the patients with post stroke pain and neospinothalamic dysfunction in the series of Boivie *et al.* (1989). These observations suggest that both dysfunction of the neospinothalamic tract and preservation of the posterior columns may be a requisite to the development of central pain syndromes. The failure of posterior column electrical stimulation to benefit our ASAS patients or other patients with central dysaesthesias (Berić *et al.*, 1988) or central pain (Long and Hagfors, 1975) is consistent with this interpretation.

Dysaesthesias developed in two of our three ASAS patients after an interval of 6–8 mths from the onset of neurological deficit. Similar intervals of time have been described for the onset of dysaesthesias following spinal cord injury (Pollock *et al.*, 1951; Davis, 1975; Davidoff *et al.*, 1987; Berić *et al.*, 1988) and anterolateral cordotomy (Pagni, 1977, 1989; Nathan and Smith, 1979). The worsening of dysaesthesias with continued posterior column electrical stimulation observed in one of our patients and in the literature (Cole *et al.*, 1987; Berić *et al.*, 1988) is consistent with the hypothetical role for dissociated sensory loss and preservation of posterior column input in the pathogenesis of this syndrome. The substantial time interval between CNS injury and the development of dysaesthesias may imply reorganization of sensory processing at a central level. Indeed, alterations in thalamic receptive fields have been observed in a patient with dysaesthesias following spinal cord injury (Lenz *et al.*, 1987). Electrical stimulation of altered thalamic regions in this patient reproduced burning dysaesthesias. A recent study has elegantly demonstrated synaptic convergence of spinothalamic and lemniscal projections upon individual thalamic neurons within the ventrobasal nuclear complex of the rat (Ma *et al.*, 1987). Further, hyperactivity of thalamic lemniscal relay neurons in the cat has been observed following spinothalamic tractotomy (Hirayama *et al.*, 1990). Our clinical and physiological evidence suggests that central dysaesthesias may develop as a result of an afferent imbalance between impaired spinothalamic and intact lemniscal sensory input. Thalamic convergence of these sensory pathways may be a likely anatomical and physiological substrate for the alterations in CNS interpretation of sensory input responsible for these dysaesthesias.

Alternative explanations for our observations also are plausible (Pagni, 1977, 1989; Tasker and Dostrovsky, 1989). Since our patient assessment was physiological rather than anatomical, we have undoubtedly underscored the potential importance of injury to anterolateral spinal pathways other than the neospinothalamic tract. Nathan and Smith (1984) suggested that dysaesthesias may result from selective lesioning of the neospinothalamic tract, sparing spinoreticulothalamic connections. These pathways are united in the spinal cord, but are distinct in the mesencephalon, perhaps accounting for the higher incidence of dysaesthesias after mesencephalic tractotomy as compared with anterolateral cordotomy (Nathan and Smith, 1984). Both clinical and radiological evidence suggests that our two patients who developed dysaesthesias had less severe lesions of the anterolateral cervical spinal cord than the patient who did not. Patients 1 and 2 with painful dysaesthesias showed substantial recovery of voluntary motor control, accompanied by the development of spasticity. Patient 3, who never developed dysaesthesias, showed no such improvement in voluntary control, and failed to manifest lower extremity spasticity, suggesting that she suffered a more complete lesion of anterolateral descending spinal pathways. Magnetic resonance imaging of the cervical spinal cord was normal in patients 1 and 2, while it was abnormal in patient 3. Davidoff *et al.* (1987) and Berić *et al.* (1988) also associated the development of dysaesthesias with incomplete spinal cord injury. If the hypothesis of Nathan and Smith (1984) is correct, then perhaps the lesions in our patients 1 and 2 spared some spinoreticulothalamic connections involved in the lesion of patient 3. We have no means of definitively assessing this in living patients. Likewise, we cannot assess the potential role of preservation of posterior spinal pathways other than the posterior columns. Painful sequelae did not complicate the clinical course of patient 3, implying that the development of dysaesthesias is not predetermined in all cases of anterolateral spinal cord infarction, as in any biological model of central pain. Posterior column afferent function was similarly preserved, while neospinothalamic afferent function was similarly absent in all three of our patients with the anterior spinal artery syndrome. Since dysaesthesias did not develop in patient 3, it is conceivable that a more extensive lesion in this patient may have affected descending control systems modulating the excitability of cells responding to afferent information. Such influences may prove to be important for the development of dysaesthesias and central pain with dissociated sensory loss.

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TEMPORAL DISCRIMINATION IS ABNORMAL IN PARKINSON'S DISEASE

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SUMMARY

Temporal discrimination thresholds (TDT) for recognition of paired sensory (tactile, auditory and visual) stimuli given over a wide range of time intervals were assessed in 44 patients with Parkinson's disease (PD) and 20 age-matched normal subjects. A significant increment in TDT for all three sensory modalities was found in PD patients compared with controls. This abnormality was greatly attenuated for about 2 h by a single levodopa/carbidopa (250/25 mg) tablet. A significant correlation was found between disease severity as assessed clinically and TDT. Patients with more severe PD had higher TDT values. The study of the peripheral median nerve and cortical somatosensory evoked potential recovery curves following double electrical stimulation of the index finger showed no differences between patients and control subjects, nor changes from 'off' to 'on' motor state which could explain the findings. These results indicate the existence of an abnormality of timing mechanisms in PD.

INTRODUCTION

The symptomatic manifestations of Parkinson's disease (PD) are mainly motor (Marsden, 1982). Subjective sensory symptoms were described by earlier investigators such as Charcot (1887) and Kinnier Wilson (1940). In some recent studies, primary sensory symptoms were found in 43 out of 101 (43%) (Snider *et al.*, 1976) and in 19 of 50 (38%) (Koller, 1984) patients with PD. Schneider *et al.* (1986, 1987) reported deficits on tests of sensory function and sensorimotor integration in the orofacial region and the arms. Disturbance of olfactory function has also been documented in PD (Ward *et al.*, 1983; Quinn *et al.*, 1987). Nevertheless, the meaning and origin of sensory and other non-motor clinical manifestations of PD is poorly understood at present. Marsden (1982) proposed a primary role of the basal ganglia in motor control while Snider *et al.* (1976) suggested that sensory symptoms in PD reflect participation of the basal ganglia in sensory function. Hassler in his scholastic review (1978) indicated that the basal ganglia served a sensorimotor integrative function, a view also held subsequently by other researchers (Cooke and Brown, 1979; Schneider *et al.*, 1982; Rolls and Williams, 1987).

One approach to the study of sensory function is the assessment of temporal discrimination. Temporal discrimination (TD) is a measure of the minimum time interval required between two successive auditory, visual or somaesthetic stimuli for them to be perceived as separate. In a previous study (Lacruz *et al.*, 1992) we found that patients with focal striatal and thalamic lesions had abnormal somaesthetic temporal discrimination thresholds (STDT), i.e. showed a prolongation of the time interval required for paired

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stimuli to be perceived as separate on the hand contralateral to the lesion. Many of these patients also showed clinical features of parkinsonism. In a preliminary study we found an alteration of STDT in PD (Obeso *et al.*, 1987). In this report we analyse in detail factors influencing STDT in a larger number of patients with PD and extend the investigation to visual and auditory TD.

SUBJECTS

The patient group consisted of 44 (30 males, 14 females) patients with PD with a mean age of 57.1 ± 9 3 yrs (41–77). None of the patients had clinical evidence of dementia or depression, and all had normal scores on the Mini Mental test (Folstein *et al.*, 1975). At the time of study none of the patients had severe tremor at rest, dyskinesias or painful dystonic postures that might have interfered with the performance of the experiment. Mean illness duration was 7.7 ± 5.9 yrs (2–25). All patients were studied in the 'off' state, 12–24 h after withdrawal of anti-parkinsonian therapy. Eleven patients also performed the tests in the 'on' state following administration of 250/25 mg of levodopa/carbidopa (p.o.).

For the purpose of clinical comparisons patients were clinically classified into three severity groups (mild, moderate, severe) on the basis of their baseline ('off' medication) parkinsonian score and in accordance with the response to levodopa therapy. Those in the *mild* group (n = 15) had stable and adequate response to levodopa ('long duration response'). Patients in the *moderate* category (n = 22) had 'wearing off' fluctuations with no or only mild 'on' dyskinesias. Patients with *severe* disease (n = 7) showed complex 'on-off' fluctuations with frequent and relatively unpredictable 'off' periods, and presence of various types of dyskinesias. The King's College Hospital (KCH) Parkinson's disease rating scale (range 0–117) was used for clinical evaluations. The mean KCH score for the clinically defined mild, moderate and severe groups was 20.7 ± 9.7, 37.8 ± 14.3 and 62.3 ± 16.2. The average age of the patients with mild, moderate or severe Parkinson's disease was respectively 57.3 ± 8.7, 57.6 ± 10.6 and 55.1 ± 7.6 yrs.

Twenty normal controls (13 males, 7 females) were also tested Their mean age was 61.9 ± 11.2 yrs (42–73) None of them had a history of physical or neurological disease.

PROCEDURES

Measurement of temporal discrimination threshold

Temporal discrimination thresholds (TDT) for somaesthetic (tactile), visual and auditory stimuli were studied using the 'method of limits' (Blackwell, 1953). The minimum time interval required for paired stimuli to be felt as separate in time was first assessed starting with an 8 ms interval for auditory stimuli and a 5 ms interval for the somaesthetic and visual stimuli, and then increasing the interval by 1 ms steps (ascending temporal discrimination threshold, ascending TDT). Subsequently, starting with an interstimulus interval 10 ms higher than the ascending TDT obtained in the ascending series, the intervals were reduced until the subject could only recognize one stimulus (descending temporal discrimination threshold, DTDT). Each series was repeated six times. As a control, paired stimuli with zero time interval were randomly interposed in the series. On each trial, the subject indicated whether one or two stimuli were felt. For each subject the appropriate intensity of the stimuli was established by obtaining the individual sensory threshold (the point at which the stimulus was just noticeable) and then using a stimulus intensity above threshold. The method is also described in detail in a preceding paper (Lacruz *et al.*, 1992). Somaesthetic temporal discrimination thresholds (STDT) were evaluated by applying a rectangular electrical pulse of 0.2 ms, with ring electrodes with an intensity three times the sensory threshold on the index finger of the hand. The two hands were tested separately. Auditory temporal discrimination thresholds (ATDT) were studied by presenting a 0.2 ms click, 60 dB above the subjective auditosensory level. The right and left ears were assessed independently. Visual temporal discrimination thresholds (VTDT) were assessed by exposing the right and left eyes separately to a red light-emitting diode (LED λ = 600 mm), 5 mm in diameter, positioned at a distance of 30 cm from the subject. This resulted in a monocular retinal stimulus of 1 degree arc.

Katzman'a test (Katzman, 1983) for attention was given at the beginning and end of the procedure, and found normal in all subjects included in this report.

Electrophysiological assessment

Sensory nerve action potentials (SNAPs) and cortical somatosensory evoked potentials (SEPs) from the scalp were recorded. The recovery curves of the peripheral nerve and cortical responses to paired pulse stimuli were measured in 15 control subjects and 15 age-matched parkinsonian patients during 'on' and 'off' periods. The characteristics of the electrical stimuli were identical to the ones used for assessing STDT. Sensory nerve potentials were recorded using surface silver-silver cup electrodes placed 2 cm apart on the wrist (over the region of the median nerve). Somatosensory evoked potentials were recorded from scalp electrodes (by the standard technique) over the contralateral parietal region with ear-linked references. Sixteen SNAPs were averaged following double stimulation at 17 different time intervals (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 100, 200 ms). The amplitude of SNAPs was taken as the largest negative-positive peak-to-peak amplitude. The SEPs were the result of averaging at least 128 potentials following paired stimuli of the index finger with interstimuli intervals of 20, 30, 40, 50, 60, 70, 80, 90, 100, 200 ms. For short (20–60 ms) interstimuli time intervals a computerized subtraction method was applied for better definition and easier measurement of the early N20-P25-N35 cortical potentials. The amplitude ratio of the second (Test Response, TR) and first (Conditioning Response CR) SNAP and SEP to paired stimuli were expressed in a curve as percentage of recovery (TR/CR×100) for each interstimuli interval.

Motor function tests

To obtain an index of slowness of movement in the patients the folowing motor tests were performed.

(1) A 40 degrees ballistic flexion movement of the wrist in response to a randomly presented auditory stimulus was used to calculate the average reaction time and movement time for 20 trials. Wrist position and the surface EMG rectified activity from forearm flexor muscles were recorded and averaged (in blocks of 10).

(2) Tapping. Patients were asked to tap with the index finger of each hand as fast as possible two white squares (2×2 cm) separated by a distance of 30 cm during 30 s. The arithmetic mean of the number of taps in six trials was calculated for analysis.

Statistics

Differences between TDT values in control subjects and patients and differences in TDT according to disease severity were analysed by the unpaired t test for unequal sample size and one-way ANOVA, respectively. The paired t test was applied to assess possible differences between right- and left-hand stimulation for somaesthetic TDT and between 'on' and 'off' motor states. Spearman's correlation was used to correlate the motor tests with TDTs. Results are given as the mean ± 1 SD.

RESULTS

Somaesthetic TDT and electrophysiological studies

In control subjects STDT values in the right hand were 39.5 ± 14.3 ms (ascending TDT) and 28.8 ± 11.1 ms (descending TDT). In the left hand STD values were 37.4 ± 13.5 ms (ascending TDT) and 27.7 ± 10.1 ms (descending TDT). In patients with PD, STDTs were significantly increased (Fig. 1). Thus, STDTs in the right hand were 118 ± 23 ms (ascending STDT) and 95.2 ± 24 ms (descending STDT). In the left hand, STDT values were 117 ± 24.7 ms (ascending STDT) and 90.3 ± 22.3 ms (descending STDT).

No significant difference was found for STDTs obtained by stimulating the right or left side of the body, in either controls or patients. As there were no left versus right differences in either group, the results are presented as the mean for both sides (Fig. 1). Results for both the ascending and descending series were significantly different in patients compared with controls (Fig. 1). Accordingly, the arithmetic mean of both values (mean threshold) is used for subsequent data presentation.

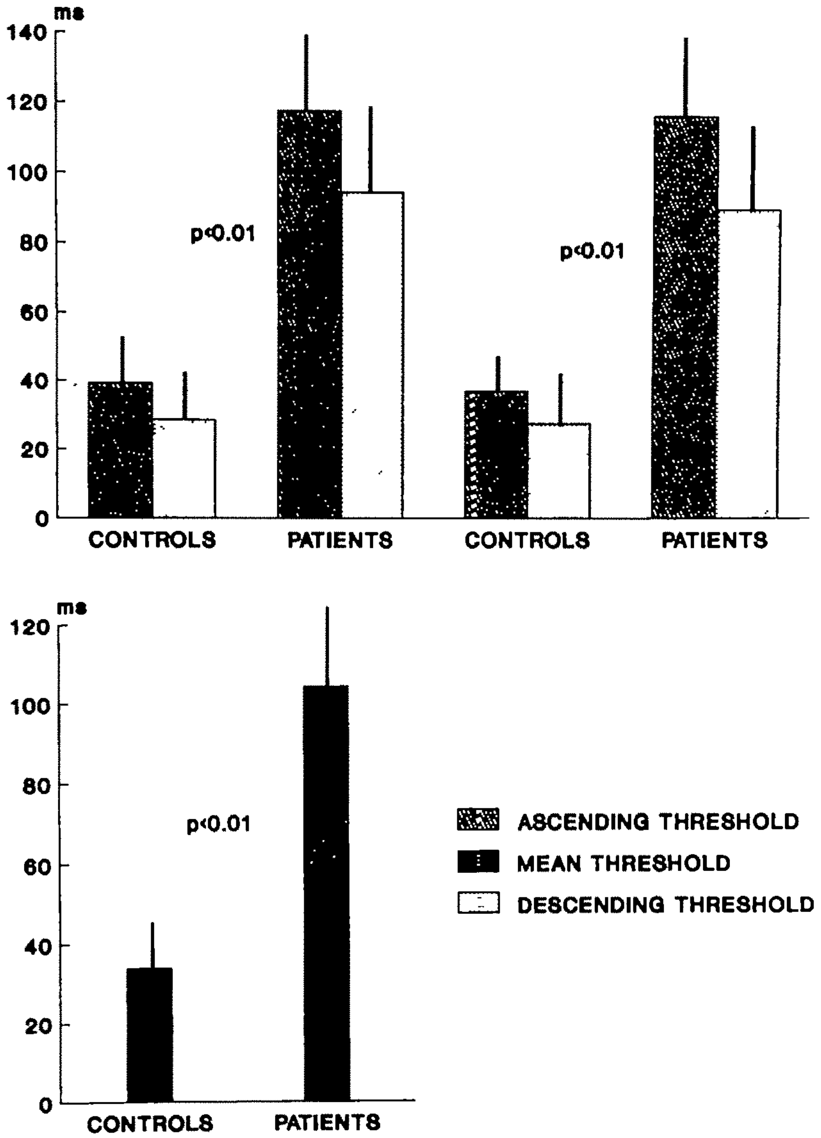

FIG 1. Somaesthetic TDT in patients with PD (n = 44) and controls (n = 20) after independent right and left index finger stimulation (*top*). Significant differences ($P<0.01$, ANOVA) between controls and patients were also obtained when data were analysed independently (right and left arm, ascending and descending series, *top*) or grouped together (*bottom*).

The recovery cycle of SNAPs was characterized by an initial phase of inhibition (refractory period) followed by a transient period of increased excitability (supranormal period) with interstimulus intervals between 5 ms and 10 ms; a second phase of relative inhibition was present with intervals between 20 ms and 50 ms (Fig. 2A).

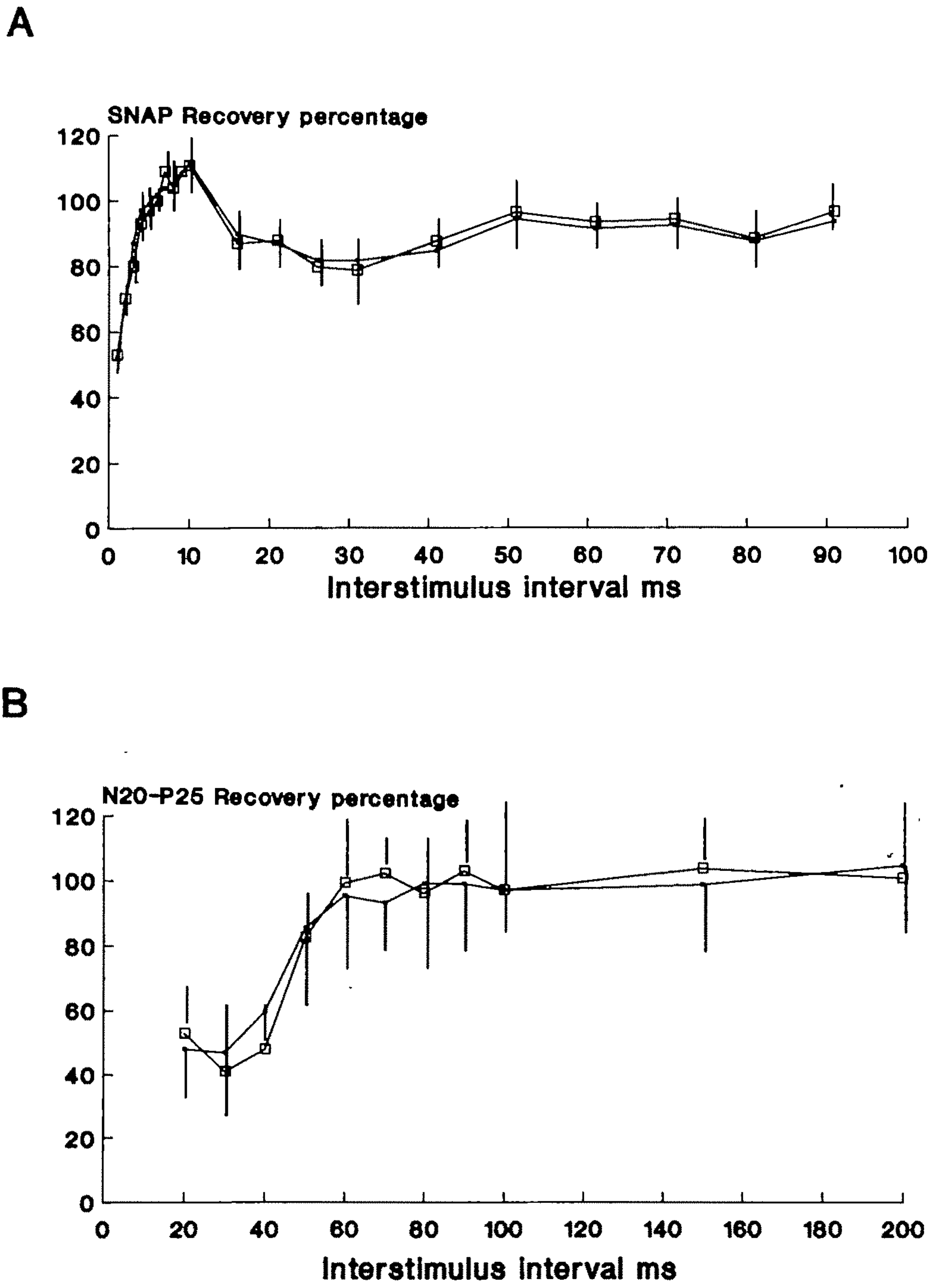

FIG. 2. Recovery curves for nerve (A) and cortical (B) evoked potentials following paired median nerve electrical stimulation in the wrist in 15 patients with PD and 15 age-matched controls No significant differences in either response was found between normal subjects (•) and parkinsonian patients (□).

A greater variability in the recovery curve of the primary response of the SEP was observed. Nevertheless, in most individuals the recovery cycle was characterized by inhibition (Fig. 2B) within the shorter intervals (between 20 ms and 50 ms) followed subsequently by a return to normal excitability (Fig. 2B). The time course of such curves is very similar to the ones previously described for a larger normal population (Gilliatt and Willison, 1963; Shagass and Schwartz, 1964). The amplitude and latency values of SNAPs and SEPs were normal in controls and patients (raw data not shown). In patients, no significant change in SNAPs and SEPs latency and amplitude was found between 'on' and 'off' periods.

Somaesthetic, auditory and visual TDT

The values obtained for somaesthetic, auditory and visual discrimination mean thresholds in 44 patients are shown in Table 1. The mean thresholds for somaesthetic, auditory and visual temporal discrimination were significantly higher for the patients compared wtih controls (Table 1). The difference between both groups was most marked for STDT. The values of TDTs for PD patients classified as mild, moderate or severe were also significantly different. Thus, for all modalities patients with more severe disease had higher TDTs (Table 1).

Motor tests and TDT

Mean reaction and movement times were respectively 288 ± 80.2 ms and 333.4 ± 45.6 ms in the 44 patients and 108 ± 16.4 ms and 102.5 ± 20.5 ms in the 20 control subjects ($P < 0.01$). The mean number of index-finger taps in 30 s was 53.3 ± 15.9 in patients and 83 ± 7.2 in controls ($P < 0.01$). A significant correlation between motor indices and TDT values was obtained in most instances (Table 2).

In the 11 patients in whom TD was evaluated before and after administration of 250/25 mg of levodopa/carbidopa, reaction and movement time were reduced, tapping frequency was increased (Table 3) and all TDT modalities, somaesthetic ($P < 0.001$), auditory ($P < 0.001$) and visual ($P < 0.001$) were significantly reduced (Fig. 3A,B,C) coinciding with the peak drug effect (around 90 min). The recovery curves of cortical and peripheral responses showed a similar pattern of 'on' and 'off' despite a reduction of STDT in the 'on' period (Fig. 3D).

TABLE 1 MEAN TEMPORAL DISCRIMINATION THRESHOLDS (ms) OF CONTROL SUBJECTS AND PATIENTS WITH PARKINSON'S DISEASE DIVIDED BY DISEASE SEVERITY AND DISABILITY (*see* PROCEDURES)

	Temporal discrimination		
	Somaesthetic	*Auditory*	*Visual*
Controls (n = 20)	33.9 ± 12	18.1 ± 7.2	68.7 ± 5.1
Parkinson's disease (n = 44)	104.1 ± 22	32.7 ± 8.8	85.6 ± 8.9
	$P < 0.01$	$P < 0.01$	$P < 0.01$
Degree of disability			
Mild (n = 15)	89.8 ± 22.7	28.8 ± 7.4	81.6 ± 9.4
Moderate (n = 22)	104.0 ± 17.4	31.4 ± 9.1	83.3 ± 6.7
Severe (n = 7)	134.4 ± 24.7	38.0 ± 11.1	92.0 ± 10.6
	$P < 0.01$	$P < 0.05$	$P < 0.05$

TABLE 2 SPEARMAN'S CORRELATION COEFFICIENT BETWEEN TEMPORAL DISCRIMINATION THRESHOLDS (TDT) AND RATING SCALE AND MOTOR INDICES IN 44 PATIENTS WITH PD

	Somaesthetic TDT	*Auditory TDT*	*Visual TDT*
KCH	0.29*	0.20	0.25*
Simple reaction time	0.47**	0.38**	0.20
Movement time	0.61**	0.42**	0.32*
Index finger tapping	−0.33**	−0.24	−0.11

*$P < 0.05$, **$P < 0.01$.

TABLE 3 MODIFICATION OF MOTOR TESTS AFTER ORAL DOSE OF LEVODOPA-CARBIDOPA (250/25 mg)

	*Tapping**		*Reaction time (ms)*		*Movement time (ms)*	
Case	*Off*	*On*	*Off*	*On*	*Off*	*On*
1	30	96	328	180	398	166
2	24	60	452	382	492	282
3	52	84	228	152	372	214
4	70	80	416	286	390	306
5	70	80	402	214	375	164
6	40	66	168	168	338	238
7	36	64	368	270	379	240
8	60	80	316	300	330	120
9	26	52	480	314	323	166
10	40	78	350	226	382	162
11	40	77	274	214	346	118
$t =$	6.85		4.80		13.17	
$P <$	0.001		0.001		0.001	

*Number of finger taps in 30 s.

DISCUSSION

The method used in this study is considered to be one of the most direct for exploration of sensory thresholds and allows repeated presentation of the stimuli (Engen, 1972). As temporal discrimination was the variable of interest, and to avoid confounding by other stimulus-related factors, the pairs of stimuli were identical with regard to other characteristics such as quality, intensity and duration. To overcome individual differences in sensory threshold, suprathreshold stimuli were used but none of the stimuli were disturbing or painful. The results obtained in the normal control group are comparable with previous studies using a similar technique (Uttal, 1959; Green *et al.*, 1961; Green, 1984).

The main finding of this study is the impairment of temporal discrimination in three different sensory modalities in patients with PD. This deficit increased with disease severity and was partially ameliorated by administration of levodopa. The abnormality in temporal discrimination in PD reported here could be related to other clinical aspects such as age of the patients and presence of cognitive impairment, or arise from dysfunction of sensory receptors or pathways. However, significant differences in thresholds were

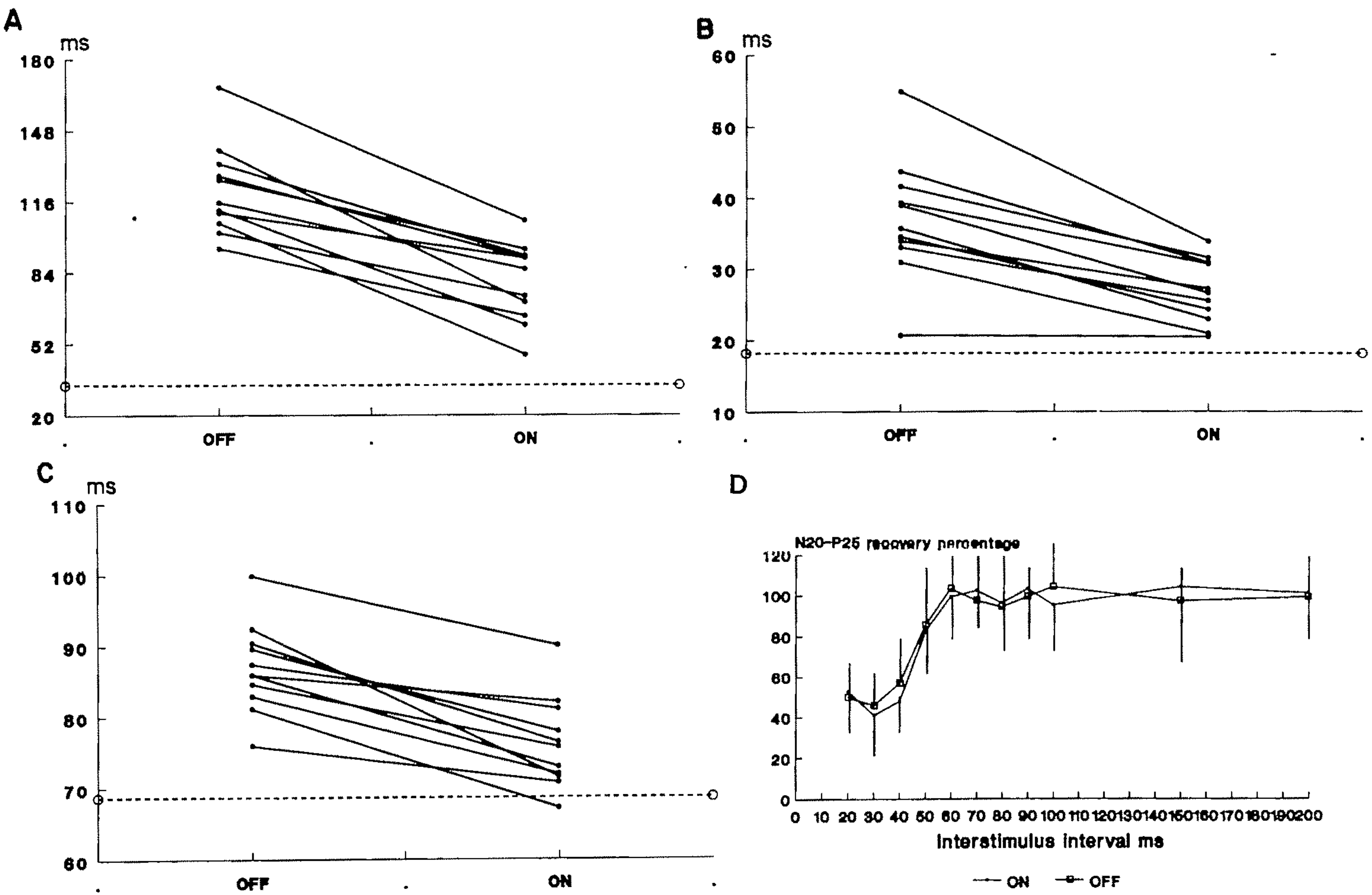

FIG. 3 Modification of somaesthetic (A), auditory (B) and visual (C) TDT from 'off' to 'on' in 11 patients with PD The horizontal interrupted lines indicate the mean normal values for each modality. D, no change in the cortical SEP recovery curve occurred in either motor state

obtained despite the fact that patients and normals were matched for age. Cognitive impairment is unlikely to have played a crucial role in the deficit of TD as one of the main selection criteria was integrity of intellectual function. Several studies have reported delayed visual evoked potentials (VEPs) (Bodis-Wollner and Yahr, 1978; Yaar, 1990) in PD. This abnormality was considered to arise as a consequence of dopaminergic deficiency in the retina (Bodis-Wollner and Yahr, 1978). However, the delay of VEPs in PD can hardly explain the impairment of visual temporal discrimination described here, which would necessitate an interference between the perception of the first stimulus and the second of each pair, not just a delay in the arrival of each of the two stimuli to the visual cortex. Furthermore, we found that abnormal STDT occurs in PD despite the presence of normal SNAPs and SEPs recovery curves following double stimulation. We believe therefore that impairment of TDT in the somaesthetic, auditory and visual modalities is unlikely to be related to any abnormality along these sensory pathways.

The anatomical basis of abnormal TDTs in PD is not entirely clear. The findings that TDT increased with the severity of PD suggest that abnormal TD is linked to the disease process. Following administration of levodopa, TDT decreased significantly, although it did not attain normal values. This can be taken as an indication that the dopaminergic system may not be solely involved in the findings described here, but dose-response curves were not performed. It might therefore be considered that the failure to achieve normal TDT values after a single levodopa dose may merely reflect incomplete dopaminergic stimulation. Theoretically, faulty dopaminergic function in PD could disturb TD by directly impairing intrinsic cortical mechanism involved in the perception and temoral distinction of paired stimuli by changing strio-pallidal output to the cortex, or both. Experimental data suggest that the dopaminergic mesolimbic system is involved in the maintenance of attention (Piazza *et al.*, 1988). Patients with PD have a deficit in attention, particularly during 'off' episodes (Gotham *et al.*, 1980). We checked for defective attention during the tests by randomly introducing stimuli with zero time interval, and Katzman's test did not reveal any major modification between 'on' and 'off'. Taylor *et al.* (1986) demonstrated that recent visual memory is normal in patients with PD, which implies a normal attention span. The characteristics of the TD tests applied in this study required a simple decision between two fixed possibilities, making the participation of a memory retrieval deficit unlikely in our patients. Thus, it seems unlikely that a general and gross defect of attention could be the main explanation for our findings.

Somaesthetic TDT values similar to those of our patients with PD were found by Lacruz *et al.* (1992) in patients with focal striatal or thalamic lesions without disruption of somaesthetic pathways or cortical damage. In intact monkeys, extracellular recording shows that few pallidal neurons respond to afferent stimuli. In fact, Miller and De Long (1988) and Filion *et al.* (1988) have demonstrated that normally internal globus pallidus (GPm) neurons discharge almost exclusively in response to passive limb movements. Such selectivity is lost following blockade of the dopaminergic pathway by reserpine (p.o.) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (i.v.) administration, leading to an increased number of GPm neurons responding to a variety of somaesthetic stimuli (Filion *et al.*, 1988; Miller and De Long, 1988). In addition, the magnitude and duration of the response is also greater (Miller and De Long, 1988). It may be deduced from such data that in PD, striato-pallidal responsiveness to peripheral stimuli is increased in magnitude and reduced in specificity. In other words, the 'noise' level provoked by sensory afferents is augmented, and this could increase TDTs. Indeed, the striato-pallidal complex has been attributed with a 'filtering' function, capable of focusing attention on one single event whilst suppressing all other non-relevant stimuli (Hassler, 1978). A more attractive and complementary explanation is that increased pallidal inhibitory output to the thalamus, as it occurs in parkinsonian monkeys (Mitchell *et al.*, 1989), provokes a reduction in the rhythmic neuronal firing of thalamo-cortical circuits acting as internal pacemakers. The existence of pacemakers or internal clocks in the CNS is well documented for many circadian functions, and presumably may also exist for time perception (Moore-Ede *et al.*, 1982). In order to differentiate as separate in time two successive stimuli, the subject must have an internal representation of time which serves as reference for events occurring in the external world. Parkinsonian patients require a longer time interval to discriminate between paired stimuli and also show an abnormal performance in many tasks which depend upon appropriate internal time estimation or rhythm generation (i.e. reaction time, sequential and alternating movements, blinking, arm swinging). We believe, therefore, that abnormal TDTs indicate that the 'internal clocks' run slowly in PD. We found a significant although not very striking correlation between TDT and motor performance. This suggests that the proposed disorder of timing mechanisms in PD might take part in the pathophysiology of bradykinesia. Patients with PD are as good as normal control subjects in modulating the amplitude and duration of the first agonist burst during a ballistic movement according to the distance and the background, but movement speed remains abnormally slow. Berardelli *et al.* (1986) suggested that such findings may be explained as a defect in motor cortex activation due to a perceptual failure to select the muscle commands to match external force/speed requirements. Abnormal timing could be added to the abnormalities involved in slowness of movement in PD (Marsden, 1982).

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TIME ESTIMATION AND REPRODUCTION IS ABNORMAL IN PARKINSON'S DISEASE

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SUMMARY

We compared the performance of 44 patients with Parkinson's disease (PD), tested 12–24 h after withdrawal of dopaminergic medication, with 20 age-matched controls, on a verbal test for time estimation and in several time reproduction tasks.

Patients with PD underestimated the duration of a time interval in the verbal time estimation task and showed overproduction of time intervals when required to reproduce a short time sample. Absolute errors were greater in the reproduction of longer time intervals in both control and PD patients, but especially in the latter. The presentation of time markers at faster rates had a detrimental effect on the performance of the patients but not of the controls. Patients with more severe PD performed worse on the time estimation and reproduction tasks compared with those with milder disease. Administration of levodopa-carbidopa (205/25 mg, p.o.) significantly reduced absolute errors in time estimation and reproduction in conditions where time markers were presented at the two faster rates of 5 Hz and 3.3 Hz. Performance in these two latter tests best discriminated patients and controls and had a positive significant association with simple reaction time and movement time. These results lead us to suggest that time estimation, i.e. the 'internal clock', is abnormally slow in PD.

INTRODUCTION

Timing is a primary aspect of movement since very few real life acts can be characterized by force attainment criteria independent of timing, and most tasks demand the production of an appropriate force-time pattern (Stelmach and Worringham, 1988). Deficits in timing are evident in most motor abnormalities reported in Parkinson's disease (PD). Thus, increased reaction time and movement time (Evarts *et al.*, 1981; Bloxham *et al.*, 1984; Stelmach *et al.*, 1986) and prolonged inter-onset latencies when performing simultaneous and sequential movements are well documented (Benecke *et al.*, 1986). Rhythm has been regarded as a possible structural basis for timing (Martin, 1972). Reports of an inability of parkinsonian patients to maintain a specific rhythm in tapping (Nakamura *et al.*, 1978; Stelmach *et al.*, 1987) is also consistent with the suggestion of a deficit in the perception and/or reproduction of the timing component of movement in PD. There is also some evidence indicating that 'timing' alterations of patients with PD may not be limited to the motor domain. A deficit in temporal somaesthetic discrimination, i.e. a prolongation of the time interval required for paired stimuli to be perceived as separate in time, has been reported in parkinsonian patients (Obeso *et al.*, 1987) and shown to be true also for temporal discrimination in the visual and auditory modalities

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(Artieda *et al.*, 1992). Recently, cerebellar patients have been found to be impaired in both motor and perceptual tasks requiring accurate timing (Smith, 1957; Ivry *et al.*, 1988; Ivry and Keele, 1989). On the basis of these findings it has been suggested that the same timing system is used in both motor and perceptual tasks (Keele *et al.*, 1985; Keele and Ivry, 1987; Ivry *et al.*, 1988; Ivry and Keele, 1989). Time estimation is therefore an aspect of perception which would be of particular interest with regard to slowness of movement in PD.

To our knowledge, this issue has only been addressed in a recent study by Ivry and Keele (1989). Time perception was assessed by judgements of whether the duration of a successive series of time intervals demarcated by a pair of tones was longer or shorter than a previously presented 400 ms standard auditory signal. Twenty-eight patients with PD tested on their normal levodopa medication showed no perceptual deficit. The fact that the PD patients were tested on levodopa medication, together with certain other unexpected findings of the study (i.e. the failure to find a deficit in finger tapping in the patients and the minimal difference in tapping performance when patients were tested 'on' versus 'off' medication), necessitates cautious interpretation of these results.

The present study was designed to assess perception of time by patients with PD. The methodology involved comparison of the performance of patients with PD with that of normal controls on a variety of time estimation and reproduction tasks. In addition, the influence of factors such as the availability of external time-keeping aids (time markers), the effect of the provision of feedback and the medication and motor status ('on' versus 'off') of the patients on reproduction of time intervals were also examined.

METHODS

Subjects

Forty-four patients (30 males, 14 females) with idiopathic PD and no clinical evidence of dementia took part in the study. All patients had scores within the normal range (above 28) on the Mini Mental test (Folstein *et al.*, 1975). None of the patients had severe resting tremors, drug-induced dyskinesias or painful dystonic cramps that may have acted as potential distractors during the experiments at the time of the study. The mean age of the patients was 57.1 ± 9.3 yrs (range = 41−77 yrs). The mean age of onset of PD was 49.5 ± 3.4 yrs (range = 40.4−51.5 yrs). The duration of illness ranged from 8 mths to 25 yrs, with an average of 7.7 ± 5.9 yrs. All 44 patients were studied in the off state 12−24 h after withdrawal of levodopa therapy. Eleven patients also performed the experimental tasks in the on state following administration of 250/25 mg (p.o.) of levodopa/carbidopa.

The King's College Hospital (KCH) Parkinson's disease rating scale (range = 0−117, higher scores = more severe disease) and the response to levodopa therapy were used to classify the patients into mild, moderate and severe disease groups. Patients in the mild group (n = 15) had a good response to levodopa. Those in the moderate category (n = 22) had predictable 'wearing off' fluctuations. Patients with severe disease (n = 7) showed complex, relatively unpredictable 'on-off' fluctuations and various types of dyskinesias. The clinically defined mild, moderate and severe groups had respectively 'off' KCH scores of 20.7 ± 9.7, 37.8 ± 14.3 and 62.3 ± 16.2. The mean age of the patients with mild, moderate and severe Parkinson's disease was respectively 57.3 ± 8.7 yrs, 57.6 ± 10.6 yrs and 55.1 ± 7.6 yrs.

A group of 20 normal controls (13 males, seven females), the majority of whom were patients' relatives, were also tested. Their mean age was 61.9 ± 11.2 yrs (range = 42−73 yrs). None of these subjects had a history of head injury, physical or neurological illness. Informed consent was obtained from all patients and control subjects prior to testing

Experimental tasks

All tests were carried out with an Apple IIe microcomputer. Subjects sat in a comfortable chair, facing the screen of a visual display unit (VDU) in an empty and quiet room, and were asked to remove their watch during testing. Subjects performed all the experimental tasks. A schematic presentation of the time-reproduction experiments is shown in Fig. 1.

1. Verbal estimation of the duration of a time interval

In this test the subject was first trained to estimate the duration of 1 s. This was done by asking the subject to count out loud at a rate of one digit per second, while looking at a hand-held watch as visual feedback. Training trials were continued until the subjects were satisfied that the duration of a 1 s interval had been internally established. During the test proper, the onset of a time interval was indicated by the appearance of a 9×10 cm rectangle on the screen. The disappearance of the rectangle from the screen indicated the end of the time interval. The subjects were required to perform the time-estimation task by internal counting of seconds as previously trained. At the end of the interval the subject was asked to give a verbal estimation (number of seconds counted) of the time interval, i.e. the interval between the appearance and disappearance of the rectangle. The time intervals to be estimated were 3 s, 9 s or 27 s in duration.

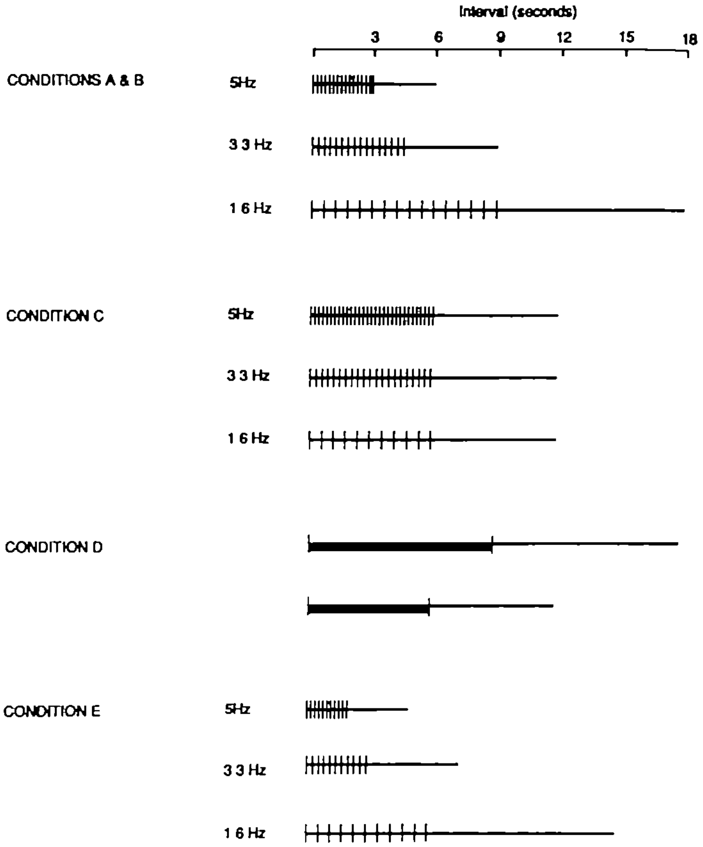

FIG 1. Schematic representation of the time reproduction tasks The first section of each line depicts the 'filled' or 'unfilled' time sample and the second section the required reproduction. The last vertical bar indicates the beginning of the time estimation period for each condition

There were 27 trials in this test, which consisted of each of the three time intervals presented nine times in a randomized order. The inter-trial interval was variable.

2. *Reproduction of time intervals*

A. Condition of 'filled' time intervals. This condition consisted of the presentation on the screen of time intervals divided equally into a series of 15 numeric time markers (numbers 1, 2, 3, 4 . . . 15 appearing on the screen). The time markers were presented at three different rates: 5 Hz, 3.3 Hz, 1.6 Hz. This resulted in time intervals of three different durations. 3 s, 4.5 s and 9 s. A block of 30 trials, with each time interval occurring 10 times in a randomized order, was presented Immediately following the presentation of the last time marker (number 15), which signalled the end of the time interval, a question mark appeared on the screen. Subjects were asked to reproduce the previous time interval by internal counting of 15 time markers at the same rate as that of the immediately preceding time samples. Subjects indicated the end of the reproduced time interval by pressing a key.

B. Condition of filled time intervals with feedback. This condition was included to assess the effect of the provision of feedback on the time estimation and reproduction tasks. This task B was identical to A above except for an additional feature. The subjects were provided with feedback on their performance at the end of each reproduced time interval The feedback was in the form of the total number of time markers that would have been counted during the time sample (maximum 15) and its reproduction (maximum 15) by the subject. Consequently, the appearance of number 30 on the VDU indicated that the time sample had been correctly reproduced by the subject. Numbers below or above 30 respectively indicated underestimation or overestimation of the time sample during its reproduction by the subject.

C. Condition of a time interval of fixed duration 'filled' with time markers presented at different rates. This condition followed the same general procedure as in condition A above. The exception was that in all 30 trials, the duration of the sample time interval was the same and fixed at 6 s. However, the sample time interval was filled with 30, 20 or 10 time markers respectively presented at the rate of 5 Hz, 3.3 Hz or 1.6 Hz. Ten trials with each time marker occurred in a randomized order. At the end of the 6 s 'filled' time sample, a question mark appeared on the VDU at which point the subject was asked to reproduce the interval by internal counting of the time markers at the immediately preceding rate.

D. Condition of an 'unfilled' time interval. This condition made it possible to assess the influence of the method of presentation of the time samples: with or without time markers. The duration of the unfilled time sample was indicated by the appearance and disappearance of a 9×10 cm rectangle as in test 1 above. At the end of the interval a question mark appeared on the screen requiring the subject to reproduce the preceding time sample. Subjects were instructed to use their own preferred strategy during reproduction of the time interval. As before, the subject indicated the end of the reproduced time interval by pressing a key. The time samples were 6 s or 9 s in duration and 10 trials of each were presented.

E. 'Condition' time reproduction test. This condition was included to check that the subjects performed the 'filled' time reproduction tasks by paying attention to the time markers during presentation of the time sample and by using internal counting of time markers at specified rates for the reproduction of the time interval, rather than relying on alternative strategies (for example, equating the duration of a time sample with a sentence or tune of a particular length and using this as a reference during the reproduction task). To this end, on each trial the time sample was shorter than the interval that had to be reproduced by the subject. The time samples were 2 s, 3 s and 6 s in duration. The subject was required to reproduce respective time intervals of 3 s, 4.5 s and 9 s. Furthermore, during the time sample 10 time markers were presented whereas the subject was asked to employ 15 time markers at respective rates of 5 Hz, 3.3 Hz and 1.6 Hz for the reproduction of the 3 s, 4.5 s and 9 s intervals. Ten trials of each time sample (2 s, 3 s and 6 s) were presented in a fixed order to all subjects.

3. *Motor speed evaluation*

The speed of movement initiation and execution was also assessed in the patient group. Patients were asked to tap with the most affected hand during 1 min, two white squares (2×2 cm) presented against a black background and separated by a distance of 30 cm. The average number of taps was calculated. In a second task, patients were asked to perform a 40 degrees flexion movement with the right wrist in response to an auditory stimulus. Wrist position and surface EMG from wrist flexor muscles were recorded in order to assess reaction time and movement time. The mean reaction time and movement time across 20 trials were computed.

Statistical analysis

In each experimental test, the absolute error in time estimation and reproduction (AETER) and the percentage of trials with underestimation or overestimation were calculated using the computer. Subjects with outlying values (±3 standard deviations from the mean) were excluded from the patient group. The raw data were transformed logarithmically to normalize the distributions. The effect of group (Parkinson's disease versus controls) and other experimental variables were examined using series of repeated measures multivariate analysis of variance (MANOVAs) tests. Paired t tests were used to assess the effects of the patient's medication status ('on' versus 'off') on the experimental tasks.

RESULTS

There were no sex differences in AETER in any test, in either the PD or control groups. The differences in age between the patients and controls were not significant ($t = 1.8$, d.f. = 62, $P = 0.8$). Age was not significantly correlated with AETER in either group.

1. Estimation of the duration of a time interval

The mean AETER for each of the three time intervals is presented in Table 1. For the PD group these data are also given separately for the three subgroups differentiated on the basis of disease severity. Patients showed a higher percentage of underestimation and had significantly greater absolute errors in time estimation compared with controls [$F(1,57) = 38.4$, $P < 0.01$]. For both patients and controls, the duration of the time sample had a significant effect on AETER [multivariate $F(2,56) = 215.1$, $P < 0.001$], with longer durations resulting in greater error. The group by duration interaction was also significant [multivariate $F(2,56) = 15.7$, $P < 0.001$], which resulted from a greater difference between the two groups on estimation of the 27 s sample than the 9 s or 3 s intervals. In the patient group, the magnitude of AETER also increased significantly with increase in the severity of illness as measured by the KCH rating [$F(2,36) = 6.9$, $P = 0.003$]. Compared with the 'off' state, levodopa produced a significant improvement in the performance by the patients of the verbal estimation task [$F(1,8) = 40.7$, $P < 0.001$].

2. Reproduction of time intervals

The PD patients performed all five reproduction tasks with higher AETER than controls (Table 2) and also had a greater percentage of overestimation. If the subjects were

TABLE 1 ABSOLUTE ERRORS ON THE VERBAL ESTIMATION TASK

	Absolute errors (ms)		
	3 s	*9 s*	*27 s*
Controls	356 ± 251	1350 ± 845	3575 ± 2334
Parkinson's disease	1828 ± 1586	3476 ± 2665	9361 ± 5012
Mild	1154 ± 794	1771 ± 1156	6778 ± 4355
Moderate	1717 ± 1014	4085 ± 2557	10757 ± 4902
Severe	4767 ± 2923	6250 ± 3673	11075 ± 5212

TABLE 2 ABSOLUTE ERRORS OF TIME ESTIMATION AND REPRODUCTION (AETER) IN THE CONTROL AND PD GROUPS FOR THE FIVE REPRODUCTION TASKS

	Absolute errors (ms)	
	Controls	*PD*
A. 'Filled' time intervals		
3 s (5 Hz)	427±227	1397±845
4.5 s (3.3 Hz)	443±228	1386±1358
9 s (1.6 Hz)	722±581	1408±1499
B. 'Filled' time intervals with feedback		
3 s (5 Hz)	330±194	1182±799
4.5 s (3.3 Hz)	315±111	784±562
9 s (1.6 Hz)	454±254	963±755
C. 'Filled' time intervals of fixed duration		
6 s (5 Hz)	590±394	2778±1665
6 s (3.3 Hz)	587±313	1858±1256
6 s (1.6 Hz)	543±519	1008±756
D. 'Unfilled' time intervals		
9 s	656±389	969±529
6 s	513±237	786±527
E Control 'filled' time reproduction		
2 s (5 Hz)	452±276	1530±1013
3 s (3.3 Hz)	585±257	1095±799
6 s (1.6 Hz)	574±365	1273±663

Duration of time intervals are shown on the left and the rate of presentation of time markers are given in parentheses.

executing the reproduction tasks using the specified strategy, no difference in AETER between the control test E and test A with 'filled' time intervals would be expected. Indeed, a comparison of the two tests revealed no differences between them [F(1,57) = 68, P = 0.41]. The group by condition interaction was also not significant [F(1,57) = 0.03, P = 0.85]. The patients with PD had significantly higher AETER than controls across both conditions [F(1,57) = 45.2, $P < 0.001$].

The effect of the experimental variables (duration of time sample, provision of feedback, 'filled' versus 'unfilled' time intervals, rate of presentation of time markers, levodopa medication) was examined by comparing the performance of patients and controls under the various experimental conditions.

A. Effect of the duration of the time sample. For the same frequency of time markers, the effects of group (patient versus controls) and duration of time samples on AETER were examined. This involved comparisons of AETER in the fixed 6 s duration (condition C) with the AETER obtained for the 3 s, 4.5 s and 9 s intervals (condition A). These data are presented in Table 2 and Fig. 2. The group by duration interaction effect failed to reach significance at the 5% level [F(1,57) = 3.5, P = 0.07]. The main effects of group [F(1,57) = 44.6, P = 0.001] and duration [F(1,57) = 7.6, $P < 0.001$] were significant. Patients had higher AETER across all durations and AETER was greater for longer time intervals in both patients and controls, but more so for the patients than controls (Fig. 2).

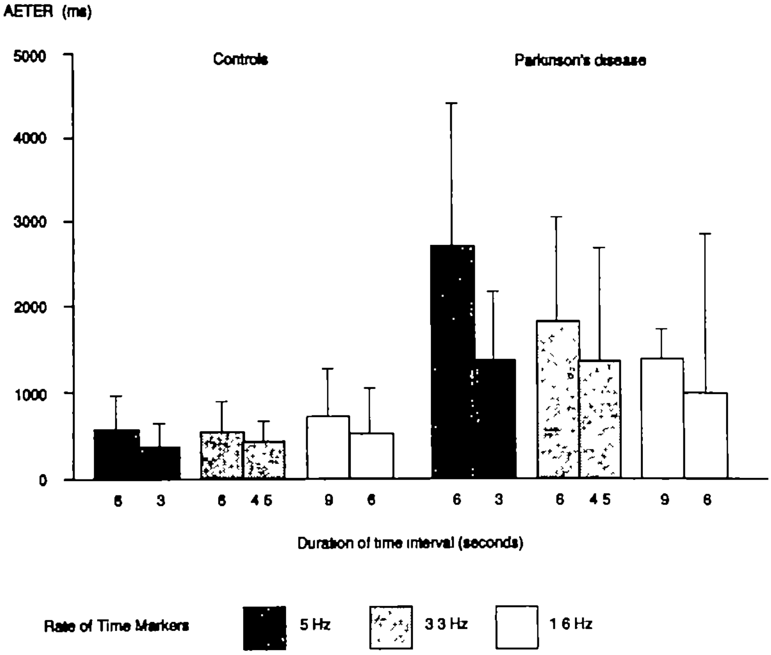

Fig. 2. Effect of the duration of the time interval on the absolute error of time estimation and reproduction (AETER) in the control and PD groups Patients showed significantly higher AETER than control for any given time interval and frequency

B. Effect of feedback. The effects of feedback on AETER was examined through comparison of conditions A and B (Table 2, Fig. 3). As expected, the main effect of group was significant [F(1,57) = 31.8, $P < 0.001$]. Provision of feedback reduced AETER and improved performance of the 'filled' interval reproduction task both in the control and PD groups [F(1,57) = 24.4, $P < 0.001$]. The group by feedback

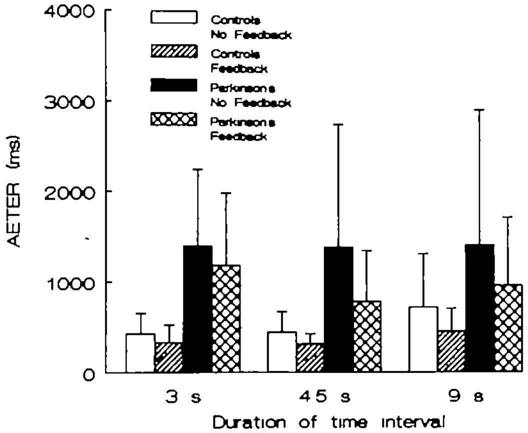

Fig 3. Effect of feedback on the absolute error of time estimation and reproduction (AETER) in the control and PD groups Both normal subjects and patients improved with feedback, but AETER were significantly higher in either condition, for any given interval, in patients

interaction [F(1,57) = 12, $P = 0.73$] and the feedback by duration interaction [multivariate F(2,56) = 47, $P = 0.63$] were not significant.

C. Effect of the frequency of time markers. Figure 4 shows the AETER obtained by the PD patients and controls in the reproduction of the 6 s time interval with time markers presented at the rate of 5 Hz, 3.3 Hz or 1.6 Hz (condition C). The main effects of group [F(1,57) = 52.1, $P < 0.001$] and frequency of time markers [F(2,59) = 11.9, $P < 0.01$] and their interaction [multivariate F(2.56) = 4.1, $P = 0.02$] were all significant. As evident from Fig. 4, presentation of time markers at a faster rate produced a differentially greater increase in AETER in the PD than in the control group.

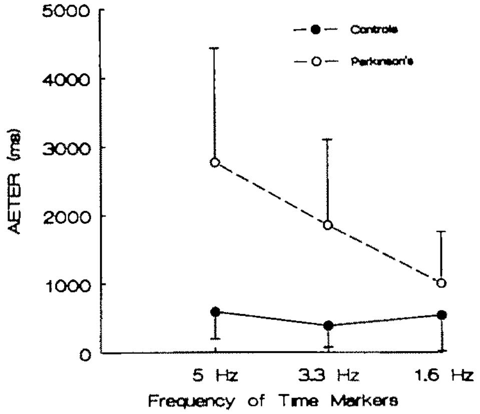

FIG. 4. Effect of the frequency of time markers on the absolute error of time stimulation and reproduction (AETER) in the PD and control groups Frequency of time markers presentation had no effect in AETER of normal subjects Patients with PD produced significantly higher AETER with faster marker rates.

D. Effect of the method of presentation of the time sample (with or without time markers). Examination of the effect of the method of presentation of the time samples ('filled' versus 'unfilled') involved comparison of the 9 s and 6 s 'unfilled' intervals in condition D with the corresponding intervals of the same duration in test A and C (respectively 'filled' intervals of 9 s and 6 s with time markers presented at 1.6 Hz). The relevant data are shown in Table 2 and Fig. 5. The method of presentation of the time sample (with or without time markers) had no effect on AETER in either the PD or control groups [F(1.57) = 19, $P = 0.66$]. The group by presentation interaction was also not significant [F(1.57) = 1.6, $P = 0.21$]. As expected from the previous analyses, the main effects of group [F(1.57) = 20.6, $P < 0.001$] and duration [F(1.57) = 13.6, $P < 0.001$] were significant. The group by duration [F(1.57) = 0.3, $P = 0.87$], the presentation by duration [F(1.57) = 33, $P = 0.57$] and the three-way interaction [F(1.57) = 77, $P = 0.38$] were not significant.

E. Effect of levodopa medication. For the various experimental conditions, the AETER obtained by the subgroup of PD patients tested in the 'off' state as well as after administration of 250/25 mg of levodopa/carbidopa (p.o.) were recorded. In general, as shown by the paired t test in Table 3, the patients' medication status had a significant effect on AETER in all conditions where time markers were presented at the two faster rates of 5 Hz and 3.3 Hz, with higher AETER when the reproduction tasks were

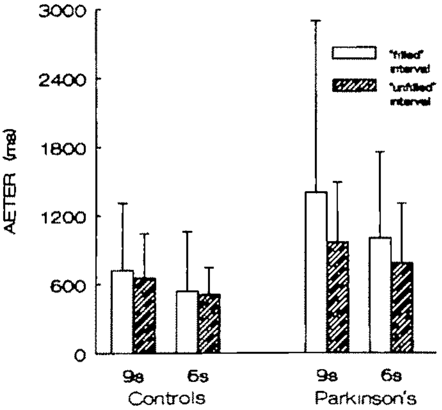

FIG. 5. Effect of presentation of time samples ('filled' versus 'unfilled') on the absolute error of time estimation and reproduction (AETER) in the control and PD groups. Both control subjects and patients performed similarly well in both conditions at the two frequencies, but AETER remained higher in patients. Visualization of the time-marker throughout the test ('filled interval') slightly increased AETER in PD patients.

performed in the 'off' state. In condition D and for the two slower frequencies in condition E there were no differences between 'on' and 'off' states.

3. *Correlation between time reproduction and motor speed*

To determine which of the reproduction tasks best discriminated the patients from controls, a stepwise multiple function discriminant analysis (SPSS PC+, 1989) was performed. Six of the reproduction tasks entered the analysis and resulted in a correct classification rate of 90%, with only four patients and two controls being misclassified. Reproduction of a 6 s time interval with time markers presented at the fastest rate of 5 Hz was the variable that entered the equation first. The distribution of AETERS from patients and controls for the latter variable were non-overlapping (Table 2).

The AETER in the reproduction of the 6 s interval, filled with time markers presented at the rate of 5 Hz, best discriminated the patients from controls, and was therefore selected for examining the association of time perception and motor speed in the PD group. Tapping, simple reaction time, and movement time had respective Pearson correlation coefficients of 0.35, 0.30 and 0.42 with AETER of the 6 s interval with 5 Hz time markers, all of which were significant ($P < 0.05$).

DISCUSSION

In time-estimation and reproduction tasks, reliance on an 'internal clock' is assumed to be a natural strategy of the subject. Internal counting has been considered to act as a regulator of the hypothetical internal clock (Fraisse, 1984). As noted by Davis (1962), the rate of counting is paramount in determining the accuracy of time estimation. As in previous work on time perception, inferences about the operation of the internal clock in normal subjects and patients with PD require two basic assumptions. First, that the rate of internal counting is accompanied by subvocalization. Secondly, that the rate of this minimal motor activity also depends on the internal clock. These two assumptions, although not directly tested in our study, are pervasive in the time-perception literature. With this proviso in mind, if the internal clock runs at the same rate as an external (objective) clock, correct time estimation and reproduction by the subject would be expected. With the internal clock running at a slower pace than objective time,

TABLE 3 ABSOLUTE ERRORS OF TIME ESTIMATION AND REPRODUCTION (AETER) OBTAINED BY PATIENTS WITH PD IN THE 'OFF' AND 'ON' STATES

	Off	*On*	*t*	*P*
A 'Filled' time intervals				
3 s (5 Hz)	1735±769	648±357	4.2	0.003
4.5 s (3.3 Hz)	1874±1598	556±394	3.2	0.01
9 s (1.6 Hz)	1600±1640	726±264	1.0	NS
B. 'Filled' time intervals with feedback				
3 s (5 Hz)	1346±808	475±223	3.7	0.006
4.5 s (3.3 Hz)	956±613	400±123	2.5	0.04
9 s (1.6 Hz)	1269±1179	482±193	0.81	NS
C. 'Filled' time intervals of fixed duration				
6 s (5 Hz)	3095±1726	982±634	3.3	0.01
6 s (3.3 Hz)	2448±1509	863±355	3.7	0.006
6 s (1.6 Hz)	1198±1099	673±528	1.3	NS
D 'Unfilled' time intervals				
9 s	1235±748	820±531	1.1	NS
6 s	803±723	406±209	1.5	NS
E. Control 'filled' time reproduction				
2 s (5 Hz)	1786±732	696±382	4.2	0.003
3 s (3.3 Hz)	973±581	680±398	1.3	NS
6 s (1.6 Hz)	1220±1013	1040±658	0.20	NS

Duration of time intervals are shown on the left and the rate of presentation of time markers are given in parentheses. NS = not significant.

underestimation and overproduction would result, while the converse would hold for the operation of the internal clock at a faster rate. This study shows that patients with PD underestimated the duration of a time interval in a verbal time-estimation task. When required to reproduce a short time sample, patients with PD showed overproduction of time intervals compared with normal controls. From these results a slowness of the internal clock in PD can be inferred.

An alternative explanation of the results could be that the observed deficits have a purely motor origin, i.e. the patients with PD were significantly slower in internal counting through subvocalization. However, the authors' personal experience upon performing these tests as well as questioning the subjects about the method used to carry out the tests led us to consider reduced subvocalization in PD as an unlikely explanation of the group differences. Nevertheless, further testing would be necessary to fully examine this possibility.

The present experimental tasks had two of the main characteristics for the adequate analysis of temporal perception, namely short time intervals and the use of the method of reproduction (Tysk, 1983). Nevertheless, other methodological limitations need to be acknowledged. Patients with PD initiate and execute movements more slowly. Thus, the use of a motor response to indicate the end of a time interval in reproduction tasks but not in the verbal estimation test, may have inflated the AETER of the patients. Simple reaction time is prolonged in PD by about 50–200 ms compared with normals (Bloxham *et al.*, 1984; Brown and Marsden, 1986; Stelmach *et al.*, 1986). However, the contribution of slowness of reaction time is likely to be minimal compared with the absolute size of the AETER in the PD group.

Consideration of the contribution of attentional processes to performance of the time-estimation and reproduction tasks is particularly important in light of the fact that deficits in attention have been demonstrated in PD, especially when patients have to rely on internal cues (Brown and Marsden, 1988). In normal subjects Wixen (1986) reported a negative correlation between 'high attentiveness' and magnitude of error in the estimation of a 3 min interval. The subject's focus of attention is also relevant since durations are judged as shorter when the estimation concerns the duration of a task than when the subject is simply instructed to pay attention to the passage of time (Curton and Lordahl, 1974). Although it is not possible to exclude the possibility that patients failed to maintain attention during time-estimation tasks, we found no abnormality in Katzman's test for attention and no defective attention was noticed in the same group of patients submitted to the temporal discrimination task (Artieda *et al.*, 1992).

Several aspects of the results of the present study replicate previous findings in normal subjects. Provision of feedback improved the performance of the reproduction task for both patients with PD and controls. Increased accuracy in the production or reproduction of relatively short durations (4 s, 12 s and 30 s) with the provision of feedback has also been reported in normal subjects by Montare (1965) and Fraisse (1971). A significant effect of the duration of the time interval on the reproduction of visual or auditory signals has been reported in normal subjects (Maloney and Calloway, 1971; Guay, 1982, 1986; Guay and Wilberg, 1983). Despite differences in the time-reproduction methodology and the specific durations of the criterion time intervals, the present results are in agreement with the findings of previous studies. For both patients with PD and controls, overestimation in reproduction of time intervals increased in magnitude with lengthening of the duration of the time sample. As in the results of Kitamura and Kumar (1983), age was not related to time estimation and reproduction in either the normal or patients group. No sex differences in time estimation and reproduction were found in either group, which also confirms the earlier findings (Kitamura and Kumar, 1983; Montare, 1985, but *see* Fraisse, 1963).

In normal subjects, use of various timekeeping aids has been found to increase accuracy and reduce variability in time-estimation and reproduction tasks (Goldstone *et al.*, 1958; Guay and Wilberg, 1983). In the present study, both patients and controls were more accurate in the reproduction of 'unfilled' time intervals than in the reproduction of time samples of corresponding duration 'filled' with time markers. Assuming that subjects also relied on internal counting at their personally preferred rate during estimation and reproduction of the 'unfilled' intervals, the present results confirm those of Guay and Wilberg (1983) showing that the addition of external visual time markers did not improve accuracy beyond that achieved by internal counting. Furthermore, the finding that overestimation by both controls and patients was greater in the 'filled' than in the 'unfilled' conditions can be explained by the 'filled-duration illusion' (FDI). This latter term refers to the fact that 'stimuli' occurring between the bounding markers of a temporal interval increase its perceived duration compared with an empty interval of the same objective duration. In addition, it has been shown that the amount of FDI increases with the number of stimuli intervening in the course of an interval and when the dispersal of the stimuli is regular rather than irregular (Grimm, 1934; Buffardi, 1971; Thomas and Brown, 1974;

Adams, 1977). In the present study, the visually presented numeric time markers which occurred at regular rates during the 'filled' time samples could have generated the FDI and hence greater overproduction in the 'filled' than the 'unfilled' intervals. The operation of the FDI is also demonstrated by the significant effect of the rate of presentation of time markers. In the fixed 6 s interval condition where 30, 20 and 10 time markers were presented at respective rates of 5 Hz, 3.3 Hz and 1.6 Hz, AETER increased with the number of time markers.

In experimental conditions where time estimation and reproduction tasks are performed through attention to, and replication of, an external tempo, accuracy depends on the extent to which the subject can generate and maintain an internal rate of counting that matches or approximates to the rate of presentation of the external stimuli. The present results show that increase in the rate of presentation of the time markers significantly inflate AETER. This confirms findings in normal subjects (Frankenhauser, 1969; Ornstein, 1969; Zakey *et al.*, 1983) where faster external tempo rates have been reported to increase inaccuracy in time-estimation and reproduction tasks. We found that faster rates of presentation of time markers also produced a differentially greater increase in the magnitude of AETER in PD patients than in controls. As evident from Fig. 4 and the significant interaction effect, the difference in AETER between patients and controls was most marked at the fastest rates of presentation of time markers (5 Hz and 3.3 Hz). These findings suggest that the patients with PD had difficulty adjusting their internal tempo to the rate of the external time markers especially when the latter were presented at the two fastest rates. This implies that the hypothetical internal clock is running at a slower rate than that set by the external tempo, leading to overproduction of the time intervals by patients with PD.

Following administration of levodopa/carbidopa, a significant improvement in time estimation and reproduction by the patients with PD was observed. This was particularly evident for the faster rates of time-marker presentation (5 Hz and 3.3 Hz). When the external time markers were presented at the slowest rate (1.6 Hz) there was no significant difference between patients tested 'on' and 'off' levodopa medication. Levodopa therefore seems to speed up the 'internal clock' of patients with PD in order to adjust the internal tempo to that of externally presented stimuli. Indeed, animal research has led to the conclusion that dopamine antagonists, such as haloperidol, and agonists, such as methamphetamine, respectively decrease and increase the speed of the internal clock (Maricq *et al.*, 1981; Maricq and Church, 1983). Some indirect evidence in support of this hypothesis also exists in the clinical literature. Whal and Sieg (1980) and Tysk (1983) have reported that chronic schizophrenics overestimate the duration of short time intervals, and that this overestimation can be reversed by treatment with neuroleptics (Wahl and Sieg, 1980). The effect of levodopa therapy in the present study also lends support to the role of dopamine in the modulation of an internal timekeeper.

The severity of PD had a significant effect on accuracy in the time-estimation and reproduction tasks. More importantly, reaction and movement times, used to quantify slowness of movement initiation and execution, were significantly correlated with the accuracy of time estimation and reproduction. These findings suggest that the timing deficit in the perceptual tasks used in this study may be related to the slowness in the initiation and execution of movements of patients with PD. Parameters best correlated with the clinical phenomenon of bradykinesia, such as inter-onset latency between two sequential movements (Benecke *et al.*, 1986), simple reaction time (Evarts *et al.*, 1981), movement time of ballistic movements (Hallett and Khoshbin, 1980; Berardelli *et al.*, 1986) and the performance of movement sequences (Nakamura *et al.*, 1978; Stelmach, *et al.*, 1987), all require appropriate timing as an essential component. Motor programs have to be quantitatively updated and temporally rearranged to match the requirements of new tasks. We therefore suggest that just as egoaesthesia (self-awareness of body parts) is required to achieve normal motor performance of the limbs (Rothwell *et al.*, 1982; Jeannerod *et al.*, 1984), an internal 'timekeeper' is also necessary to achieve adequate movement execution. The existence of a timekeeping centre in the inferior parietal lobe has been proposed by Tanaka *et al.* (1987) following a detailed study of a patient with pure word deafness. However, on the basis of the limited anatomical knowledge available at present, it is more likely that the brain possesses several timekeepers at different locations. For instance, circadian rhythmicity for drinking, sleep and temperature depends upon the integrity of the hypothalamic suprachiasmatic nuclei (Stephan and Nuñez, 1977). More recently, Ivry and Keele (1989) suggested that the lateral region of the cerebellum would play a paramount role as a timekeeper. Thus, the issue of the number and 'location' of internal timekeeping processes remains open to further research.

The findings presented in this paper indicate that internally-generated rhythms used as self-reference for time perception are slow in PD. This may be associated with reduced ability to detect the timing of two events and also in decreased capacity to generate sequences of movements at a normal speed.

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NERVOUS CONTROL OF EYELID FUNCTION

A REVIEW OF CLINICAL, EXPERIMENTAL AND PATHOLOGICAL DATA

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The authors dedicate this article to Professor Otto Stochdorph on the occasion of his 75th birthday

SUMMARY

This review of the clinical and experimental literature on pre-motor eyelid control, including an analysis of available clinico-pathological reports, suggests support for the following hypotheses: (1) cortex, extrapyramidal motor systems and rostral brainstem structures contribute to the control of the levator palpebrae muscle (LP) in various eyelid functions; (2) though the LP motor nucleus is unpaired, the pre-motor control of LP is at least in part lateralized; (3) signals of the rostral interstitial nucleus of the medial longitudinal fasciculus (MLF) are involved in the control of coordinated lid movements with saccadic up- and downgaze movements; (4) lesions of the medial and/or principal portion of the nuclear complex of the posterior commissure are essential for the production of lid retraction. These structures are assumed to be involved in lid-eye coordination by providing inhibitory modulation of LP motor neuronal activity; (5) the ventral periaqueductal grey is assumed to play a role in the generation of tonic LP motor neuronal activity; (6) neurons of the caudal supraoculomotor area could play a role in the mediation of converging inhibitory inputs onto LP motor neurons.

INTRODUCTION

Contemporary oculomotor research has focused mainly on eye movements, while the pre-motor control and disturbances of the upper eyelids have received little attention. The first study on conjugate lid movements dates back to the last century (Gowers, 1879), but still almost nothing is known about the neuroanatomy of the pre-motor connections controlling the principal lid muscle, levator palpebrae superioris. The present article describes the normal functions of the eyelid, then reviews the pre-motor disturbances of eyelid control and discusses the existing evidence on the nervous control of levator palpebrae. Special emphasis is placed on the symptom lid retraction. We have re-analysed the lesions of eight selected, previously published clinico-pathological cases in order to outline more closely the critical region for the production of lid retraction. In the light of the reviewed evidence, we formulate hypotheses on the pre-motor control of levator palpebrae.

NORMAL FUNCTION OF THE EYELIDS

Elevation of the upper eyelid and control of its vertical position is subserved by the levator palpebrae muscle (LP); cessation of LP motor neuronal activity causes the eyelids

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to close. The levator palpebrae is situated above the superior rectus muscle in the roof of the orbit. Its origin is attached to the lesser wing of the sphenoid bone, and its insertion is connected to the superior tarsal plate, corium, ligaments and septa of the lid. A small bundle of sympathetically innervated smooth muscle fibres, the tarsal, or Müller's, muscle, plays a role in adjusting the width of the palpebral fissure. Its origin is embedded in LP, and it inserts mainly on the tarsal plate (Landolt, 1985). Two further muscles, innervated by the facial nerve, act on the eyelid: the frontalis muscle which helps to retract the lid in extreme upgaze, and the orbicularis oculi muscle (OOc) which enables rapid and firm eye closure.

The levator palpebrae can be considered as the seventh extraocular muscle. It is innervated by the superior division of the oculomotor nerve. It differs from the oculorotatory muscles in that it contains only singly-innervated fibres, of the types suitable for fatigue-resistant tonic activity (Porter *et al.*, 1988; Spencer and Porter, 1988). Phylogenetically, LP is a comparatively new development, present in mammals but not in birds and reptiles. It evolved by separating from the superior rectus muscle, and differentiates from it at a late stage of embryogenesis (Gilbert, 1957).

The role of the upper eyelid, or lid, as protector of the eye comprises a number of separable functions: (1) tonic lid elevation when the eyes are open; (2) voluntary eye closure and eye opening; (3) involuntary adjustment of the eyelid to the vertical globe position, i.e. lid-eye coordination; (4) periodic and reflex blinking; (5) firm eye closure in protective and expressive acts, e.g. sneezing. In (1)–(3) only LP is active, in (4) and (5) different parts of the OOc contract while LP is synchronously inhibited. Accordingly, lid position, gentle eye closure and lid-eye coordination are unaffected by facial nerve palsy, while blinking and firm eye closure are impossible.

Tonic lid elevation

There is a close relationship between the tonic activity of LP and the level of alertness. Upon general activation, the palpebral fissure widens by up to 2 mm (Kennard and Glaser, 1964). With lids closed, any arousal elicits electrical activity in LP motor units (Loeffler *et al.*, 1966). The lids lower involuntarily with increasing fatigue, and at a certain stage of fatigue, it becomes impossible to keep them from closing. During sleep, including REM-phases, and when the eyes are gently closed, LP activity ceases completely.

Voluntary lid control

Voluntary control of LP always affects both lids synchronously (Gay *et al.*, 1967). Its accuracy is far more restricted than in involuntary lid-eye coordination: for example, winking is not totally unilateral, and partial bilateral lid closure causes lid tremor. Origin and course of cortical projections subserving voluntary control of LP are incompletely known. Eye opening together with globe and head movements can be evoked by electrical stimulation of wide areas of the frontal, temporal and occipital cortex (*see* Cogan, 1972; Caplan, 1974). Lesions to a similar broad range of areas can lead to cerebral ptosis or dysfunction of voluntary lid control (*see below*). The preponderance of right side lesions suggests a dominance of the right hemisphere in lid control.

Lid-eye coordination

In all types of vertical gaze changes, the lids follow the globes closely, providing maximal coverage, i.e. protection at all times (Björk, 1955; Kennard and Smyth, 1963;

Allik *et al.*, 1981; Evinger *et al.*, 1984). The two lids perform these movements in almost perfect synchrony, copying saccadic and smooth pursuit vertical eye movements in all details of their temporal and velocity profile, which is reflected in their electromyogram (Becker and Fuchs, 1988). Upon extreme downgaze, activity ceases completely (Björk and Kugelberg, 1953).

It is not quite clear how the lids are lowered with downgaze saccades. Levator palpebrae relaxes well before the beginning of the saccade, but parallel OOc activity could not be demonstrated. Therefore, elastic forces are thought to pull the lid down (Gordon, 1951; Evinger *et al.*, 1984). However, it has been argued that a brief parallel contraction of parts of the OOc may have escaped attention (Becker and Fuchs, 1988).

Blinking

In all kinds of blinks LP is abruptly inhibited, then resumes its prior level of activity without overshoot (Becker and Fuchs, 1988). In parallel to this, the palpebral portion of OOc contracts. The inhibition of LP precedes and outlasts OOc by about 10 ms (Gordon, 1951; Van Allen and Blodi, 1962; Becker and Fuchs, 1988). Conversely, OOc activity precedes and outlasts LP inhibition upon firm eye closure (Esteban and Salinero, 1979).

The dynamics of periodic, i.e. spontaneous, and voluntary blinks are very similar, except that the lids usually lower further in voluntary blinks (Gordon, 1951; Van Allen and Blodi, 1962; Kennard and Glaser, 1964). Electrical stimulation of various cortical and subcortical areas can elicit blinks; during visual attention, they are suppressed. The frequency of periodic blinks was shown to depend highly on the affective, attentional and cognitive state (Cramon and Zihl, 1977; Cramon, 1980). Central dopaminergic activity is likely to play a crucial role in the generation of periodic blinks: their frequency was shown to be decreased in schizophrenic patients who received dopamine antagonists and in untreated parkinsonian patients, while it was increased in monkeys and in parkinsonian patients following administration of dopamine agonists (Karson, 1983).

In mechanically triggered blinks, OOc electromyograms display two consecutive responses (R1 and R2; Kimura, 1988), thought to reflect an early monosynaptic and a late polysynaptic activation. During R1 and R2, LP remains continuously inhibited. In low-intensity stimuli, however, the biphasic OOc response can be mirrored in the LP electromyogram: following an initial brief pause, the levator resumes activity for a short period equivalent to the latency between R1 and R2 (Esteban and Salinero, 1979). This LP pause was reported in man to appear at lower stimulation threshold than the OOc response (Bratzlavsky, 1975).

In adults with oculomotor apraxia, head jerks are less conspicuous than in affected children, but gaze changes are usually accompanied at least by an eyelid blink (Cogan, 1953). Obviously, the blink in some way facilitates the generation of a saccadic eye movement; however, the mechanism is not clear. Any inhibition of omnipause neurons, lying on the pontine midline, would facilitate the generation of a saccade or gaze shift, since they exert a tonic inhibition on the saccadic generation network, and only when they are silenced can a saccade take place. One possibility is that in oculomotor apraxia blinking reduces the facilitation of omnipause neurons by visually driven inputs, for example via the monosynaptic inputs from superior colliculus (Büttner-Ennever *et al.*, 1988; Munoz and Guitton, 1989). This partial inhibition of the omnipause neurons would then allow the defective saccadic drive signal to complete the inhibition and to generate the eye movement.

DISORDERS OF LEVATOR PALPEBRAE FUNCTION

The eyelid is controlled by several different neural systems. For example, the cerebral cortex is associated with the voluntary control of the tonic level of levator activity, in particular the right side, whereas extrapyramidal dopaminergic circuits influence the execution of blinks, and the region of the nuclear complex of the posterior commissure is involved in the coordination of the lid with eye movements (*see below*). In accordance with the principle of distributed control, disturbances of eye-lid control usually affect only one type of function. Exceptions are rare and involve extensive brainstem lesions (e.g. Keane, 1975).

Nuclear ptosis

Lesions of central caudal nucleus (CCN), that is the subgroup of the oculomotor nucleus containing levator motor neurons (*see below* Nervous control of eyelid function: motor neurons and Fig. 1), cause bilateral ptosis. It is a very small region, and there are few reports of isolated lesions to it. Less rare are cases of ptosis associated with nuclear ophthalmoplegia, i.e. with additional involvement of the adjacent motor neuron subgroups. An example is a case of transient complete bilateral ptosis due to an asymmetric midbrain infarct which extended into the area of CCN mediocaudally (Growdon *et al.*, 1974). Bogousslavsky *et al.* (1983) described bilateral ptosis in a paramedian caudal midbrain infarct that presumably infringed upon the right border of CCN. Cases of ptosis from midbrain infarctions that initially, or solely, involved CCN were reported by Caplan (1974), Meienberg *et al.* (1979), Zackon and Sharpe (1984) and Dehaene *et al.* (1985). Conway *et al.* (1983) noted complete bilateral ptosis in a patient with inflammatory changes in the area of CCN. Unilateral ptosis from brainstem lesions occurs only when the intracerebral fascicles of one oculomotor nerve are damaged (Weber- or Benedict-syndrome; Tsuchida, 1906; Collier, 1927, case 2; Segarra, 1970). Observations of asymmetrical nuclear ptosis may be explained by additional lateralized damage to CCN axons.

Supranuclear ptosis

Lesions to pathways coursing in the floor of the third ventricle and in the rostral mesencephalon can lead to mild uni- or bilateral reduction of LP tonus, analogous to cerebral lesions. Otherwise, in all other cases of brainstem lesions, ptosis is the result of damage to CCN or a central Horner's syndrome (Schuster, 1921, case 1; Duke-Elder and Scott, 1971; Caplan, 1974; Halmagyi *et al.*, 1978, case 1; Moffie *et al.*, 1983, case 1). Bender and Shanzer (1964) stated that incomplete ptosis can occur in clinical and experimental MLF lesions, but no ptosis was reported in subsequent, more specific, monkey studies (Pasik and Pasik, 1975; Evinger *et al.*, 1977). Ptosis of unknown origin was noted in 10 out of 70 cases of parkinsonism (Corin *et al.*, 1972).

Cerebral ptosis

Ptosis can occur as a mild transient symptom of hemispheric infarction, mostly in extensive right-sided or in bilateral frontal lesions. The ptosis is usually bilateral (Krohel and Griffin, 1978; Lepore and Duvoisin, 1985; Lepore, 1987), but it can affect mainly, or even exclusively, the contralateral lid after lesions to cerebral cortex (Duke-Elder and Scott, 1971; Caplan, 1974) or cortico-nuclear pathways (Lowenstein *et al.*, 1987).

Dysfunction of voluntary lid control

Dysfunction of voluntary lid control can manifest as an inability to initiate lid opening or lid closure, or difficulty in sustaining lid closure. Blinking, lid-eye coordination and eye closure during sleep remain undisturbed in these conditions. A defect in voluntary eye closure ('apraxia of eye closure') and the inability to keep the eyes closed ('closing impersistence') are observed mainly in focal or diffuse hemispheric damage. Examples are cases of encephalitis (Schilder, 1926), Creutzfeldt-Jakob disease (Ross Russell, 1980), cortical angioma (Monaco *et al.*, 1980) and stroke (Berlin, 1955; Joynt *et al.*, 1962; Lessell, 1972; Rosati *et al.*, 1978; Dehen and Cambier, 1979; Colombo *et al.*, 1982), but also of progressive supranuclear palsy (PSP) (Jankovic, 1984; Golbe *et al.*, 1987). Occasionally, only one lid is affected (Berlin, 1955; De Renzi *et al.*, 1986). Effective unilateral lesions are practically always on the right side. Since an inability to close the eyes often turns into closing impersistence, both symptoms are likely to have a common basis. Gentle eye closure being brought about by inhibition of LP, disorders of voluntary lid closure are likely to be due to a deficit of cortical inhibition of LP, rather than of OOc activation.

Patients with a defect in voluntary eye-opening may find it impossible for seconds, minutes or even permanently to reopen both eyes, though OOc is inactive. They may, however, be able to open the eyes upon a sudden command or stimulation. Once they succeed, the eyes remain open without ptosis. Lid-eye coordination is usually undisturbed and the eyes reopen normally after a blink. A typical case was reported by Bechterew in 1898: a woman could not prevent her lids falling down slowly, though upon distraction they would intermittently elevate completely. This symptom is mainly observed in diseases of the extrapyramidal motor system, e.g. idiopathic, postencephalitic and MPTP-induced parkinsonism, Huntington's disease, Wilson's disease, Shy-Drager syndrome and, particularly, PSP (Van Allen and Blodi, 1962; Cogan, 1974; Scully *et al.*, 1975; Dehaene, 1984; Jankovic, 1984; Lepore and Duvoisin, 1985; Brusa *et al.*, 1986; Golbe *et al.*, 1987; Katz and Rosenberg, 1987; Keane, 1988). It was also seen following a unilateral therapeutic lesion in the area of the prerubral fields or the H-field of Forel (Nashold and Gills, 1967). It is rarely present in hemispheric lesions (Colombo *et al.*, 1982; De Renzi *et al.*, 1986; Lepore, 1987). The term eyelid opening 'apraxia' (Goldstein and Cogan, 1965) should be dismissed since the executive motor system is affected.

Disturbances of blinking

A decreased rate of periodic blinking is seen in PSP patients (Pfaffenbach *et al.*, 1972), in parkinsonism and in patients receiving medication with dopamine receptor blockers (Karson, 1983). In patients with parkinsonism, timing and reciprocity of LP and OOc activity were found to be disturbed during blinks. Co-activation or tremor-like rhythmic reciprocal activity of LP and OOc was present upon light lid closure, while lid-eye coordination remained intact (Van Allen and Blodi, 1962; Loeffler *et al.*, 1966). This suggests that, in addition to their influence on blink frequency (*see above* Normal function of the eyelids: blinking), dopaminergic basal ganglia circuits play a role in the inhibition of LP during blinks and eye closure.

Synkinetic lid movements

Following acute and, sometimes, chronic third nerve lesions, various synkinetic ocular, pupillary and eyelid movements can occur upon attempted gaze changes. In particular, the eyelid on the affected side can elevate with eye movements directed inwards or downwards. Such lid elevation with downgaze has been termed pseudo-Graefe sign. As in synkinetic facial movements following seventh nerve palsy, it is commonly believed that synkinetic ocular movements result from misdirected regenerating third nerve fibres. This view was challenged by the suggestion that synkinesis may originate from ephaptic neuronal transmission at the site of nerve injury, or from synaptic reorganization of retrogradely affected oculomotor neurons (Lepore and Glaser, 1980; but *see* Miller, 1985*c*).

Lid nystagmus

Lid nystagmus, a slow downward drift of the lids with correcting upward flicks, can occur upon lateral gaze or convergence. This phenomenon appears to be related to the slight elevation of the eyelids upon lateral gaze and convergence seen as a physiologic synkinesis in many normal individuals (Ticho, 1971). Lid nystagmus caused by convergence was also seen in cases of ill-definable cerebellar and/or brainstem damage (Sanders *et al.*, 1968; Rohmer *et al.*, 1972, case 3; Safran *et al.*, 1982). Lid nystagmus beating synchronously with horizontal globe nystagmus has been associated with diffuse brainstem and cerebellar symptoms (Sittig, 1917), a lateral medullary syndrome (Daroff *et al.*, 1968), cerebral trauma (Rohmer *et al.*, 1972, case 3) and a cystic cerebral lesion (Orzechowski and Jakimowicz, 1934). A possibly related phenomenon is tonic lid retraction upon lateral gaze, noted in a case of the dorsal midbrain syndrome (Christoff *et al.*, 1960). Irregular lid tremor or lid flutter upon light eye closure can occur in parkinsonism (Loeffler *et al.*, 1966) and metabolic diseases, e.g. juvenile Gaucher's disease (Nishimura and Barranger, 1980).

Lid-eye coordination in pathological eye movements

Lid-eye coordination is preserved in most pathological eye movements. In vertical nystagmus, the lids usually follow the eye movements synchronously. Rhythmic change of LP activity in this condition was demonstrated electromyographically (Björk, 1955). A persistence of lid nystagmus after vertical nystagmus had subsided was reported by Rohmer *et al.* (1972, case 1). In some cases of large pontine and caudal midbrain infarction, comatose patients exhibited permanently open eyes with continuous vertical eye movements accompanied by synchronous lid movements (Keane, 1975, case 1; Stacy, 1982; Brusa *et al.*, 1984).

In incomplete vertical gaze paralysis, the lids remain coordinated with globe movements to the preserved vertical direction; attempted gaze in the disturbed direction can cause a lid saccade although the globes remain immobile. Related phenomena were observed in an experimental dorsal midbrain syndrome in the monkey. Upon vestibular stimulation, the lids elevated rhythmically, while a normal upbeat nystagmus of the globes was abolished. During episodes of vertical globe nystagmus, the eyes failed to move above the horizontal meridian, while the lids made full excursions (Pasik *et al.*, 1969*b*).

In the 'locked-in' syndrome, produced by large ventral pontine infarctions, LP tonus and control are typically preserved, together with vertical eye movements (Kömpf, 1982).

Paradoxic lid movements

Vertical eye movements that are associated with inverse lid movements are a peculiar and rare sign reported in some cases of brainstem damage. Namely, lid retraction was seen simultaneously with jerky downgaze saccades in large pontomedullary lesions (Luce, 1899; Keane, 1978), in the dorsal midbrain syndrome (Corbett *et al.*, 1981, case 3) and in a small upper right midbrain infarction (only ipsilaterally; Greenberg and DeWitt, 1983). These observations made in acute and central lesions are to be differentiated from the unilateral pseudo-Graefe sign seen in cases of third nerve damage (*see above* Disorders of levator palpebrae function: synkinetic lid movements).

Lid retraction and lid lag

Neurogenic lid retraction must be differentiated from peripherally induced lid signs, i.e. myopathic lid retraction [myotonia, myositis, dysthyroid ophthalmopathy (Graefe's sign), myasthenia (Kansu and Subutay, 1987)]; lid lag in dysthyroid ophthalmopathy or Guillain-Barré syndrome (Neetens and Smet, 1988); pseudo-Graefe sign; lid retraction due to sympathetic overexcitation and pseudoretraction due to contralateral ptosis (Lohman *et al.*, 1984).

There are no electromyographic studies on neurogenic lid retraction, but it is commonly assumed to be caused by overexcitation (disinhibition) of LP. Pasik and Pasik (1975) proposed that lid retraction in a monkey with a pretectal lesion was due to sympathetic disinhibition. Their main argument was a unilateral reduction of lid retraction after excision of the ipsilateral superior cervical sympathetic ganglion. Disinhibition of Müller's muscle, though, could not account for the presence of lid lag in monkeys and human cases (*see below*), and it appears questionable whether contraction of Müller's muscle could cause tonic lid retraction to the degree often seen in the dorsal midbrain syndrome. Lid retraction finally is a comparatively frequent sign in parkinsonism, where disturbances of sympathetic control of the pupils are rare (Corin *et al.*, 1972).

Neurogenic lid retraction (Collier's sign) is the most frequent pre-motor lid dysfunction. The lids are tonically elevated above the upper margin of the iris, uncovering the sclera (Askenasy *et al.*, 1953; Furtado, 1956; Christoff *et al.*, 1960; Cogan, 1974; Bender *et al.*, 1981; Corbett *et al.*, 1981). Relaxation of LP in blinking, eye closure and sleep is preserved. Collier (1927) first described this so-called 'tucked lids' in association with a case of vertical gaze paralysis due to a unilateral paramedian capsulo-thalamic haemorrhage, involving fibres of the posterior commissure (PC, *see* Fig. 3). In general, this type of lid retraction is bilateral, and is evident when the patient looks straight ahead. In cases with unilateral lesions, LP disinhibition is usually incomplete, i.e. lid-eye coordination still functions: the lids elevate further upon attempted upgaze, and lower upon downgaze. In rare human and experimental cases, lid retraction is seen in combination with lid-lag: the lids hesitate or fail completely to lower with downgaze (André-Thomas *et al.*, 1933; Smith *et al.*, 1959; Carpenter *et al.*, 1970; Keane, 1975, case 1; Pasik and Pasik, 1975). The lesions in these cases were generally bilateral, or unilateral and supplemented by PC lesions.

Lid retraction is typically associated with rostral brainstem or pretectal lesions. It is generally accompanied by conjugate gaze deficits characterizing the dorsal midbrain syndrome (except in cases of parkinsonism: *see* Goldstein and Cogan, 1965; Smith, 1966; Corin *et al.*, 1972; and PSP: *see* Pfaffenbach *et al.*, 1972). A broad range of processes (e.g. pinealomas, infarction, hydrocephalus) can produce the dorsal midbrain syndrome (also called Parinaud's-, Sylvian aqueduct- or Koerber-Salus-Elschnig syndrome, or syndrome of the PC; *see* Keane, 1990, for a discussion of aetiology and terminology). Its core symptoms are pupillary disturbances, conjugate upgaze and convergence paralysis. Further possible signs are: retraction-nystagmus or -spasm on attempted upgaze; downgaze paralysis; vertical nystagmus; skew deviation and fixation disturbances. While voluntary gaze and all rapid voluntary eye movements are abolished, smooth pursuit may be preserved and vestibularly-induced eye movements (doll's head reflex) are always intact. Convergence, convergence spasms or retraction spasms, where present, can be accompanied by rhythmic lid elevation (Spiller, 1905, case 5; Christoff *et al.*, 1960; Rohmer *et al.*, 1972). Lid retraction as the only persisting sign in a case of previously complete Parinaud's syndrome was reported by Orzechowski and Jarzymski (1934).

NERVOUS CONTROL OF EYELID FUNCTION

Motor neurons

In accordance with their common phylogenetic origin, LP and superior rectus motor neurons lie close together. Their axon fascicles course together, while other oculomotor axons are distributed across the profile of the oculomotor nerve (Miyazaki, 1985). Some early authors (Perlia, 1989) proposed a rostral and dorsal, ipsilateral representation of LP motor neurons in humans within the oculomotor nucleus (*see* Fig. 1), others assumed that they were located caudally, based on clinico-pathological studies (Bach, 1899; Monakow, 1905). The latter were supported by subsequent anatomical and physiological studies (Szentágothai, 1942*a*; Bender and Weinstein, 1943; Danis, 1948). In his classic degeneration study of the primate oculomotor nucleus (OMN), Warwick (1953*a*) showed that the unpaired central caudal nucleus constitutes the motor neuronal pool for both LPs. The term central caudal nucleus (CCN) was first used by Tsuchida (1906), who characterized it as a 'medial wedge-shaped nucleus of the ventral periaqueductal grey'. It is apparently identical to the 'nucleus posterior dorsocentralis' of Panegrossi (Warwick, 1953*b*). The central caudal nucleus is situated at the dorsal caudal pole of the OMN, adjacent to the medial rectus- and superior rectus subdivisions (Figs 1, 2), and rostral to the trochlear nuclei which contain the motor neurons of the superior oblique muscle. The central caudal nucleus is an integral part of the OMN, but is a recent development compared with the other, phylogenetically ancient subgroups. Its development in species with broad-range stereoscopic vision is likely to reflect the necessity for a close synchrony of both lids and the eyes. Only in higher mammals (monkey, cat, dog, horse, etc.) do the LP motor neurons form an unpaired motor nucleus on the midline (Figs 1, 2), while in rodents the motor neurons of each LP lie contralaterally, close to the superior rectus subdivision, on the lateral border of the OMN (Akagi, 1978; Glicksman, 1980; Murphy *et al.*, 1986; Evinger *et al.*, 1987). Within CCN, motor neurons of both LP are completely intermixed; a unique condition among all paired skeletal muscles (*see* Fig. 2*d*). Some findings even suggest that single motor neurons innervate both LP. In the cat, May and Baker (1987) found that individual LP motor neurons could be antidromically activated from both LP. This could explain why Warwick (1953*a*) noted that always less than half of the CCN neurons degenerated after unilateral LP resection, and why

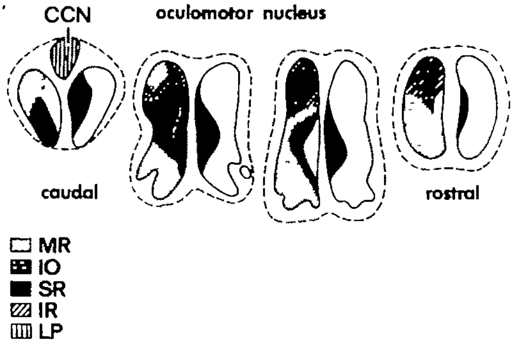

FIG. 1 Diagram of the location of motor neuron pools of individual eye muscles in the oculomotor nucleus of the monkey. The LP motor neuronal pool forms the central caudal nucleus (CCN). The stippled line indicates the area containing small motor neurons outside the classical oculomotor nucleus. MR = medial rectus muscle; IO = inferior oblique muscle; SR = superior rectus muscle, IR = inferior rectus muscle, LP = levator palpebrae muscle.

the majority of motor neurons in CCN are indeed labelled upon unilateral HRP injections into LP (Porter *et al.*, 1988; personal observations).

Lateralization of LP pre-motor control

Both lids move synchronous in normal and pathological conditions. However, pre-motor disorders do not always affect both lids equally (e.g. Blobner, 1938; Keane, 1975; Bender *et al.*, 1981). Cerebral ptosis, disturbances of voluntary lid control, lid retraction and lid lag can be unilateral or asymmetric. Unilateral lid retraction can be elicited with stimulation of the periaqueductal grey (PAG) (*see* Fig. 3) dorsal to the caudal OMN in humans (Nashold and Gills, 1967) and monkeys (personal observation). If one eye is vertically displaced (e.g. in strabismus), the positions of the lids can be adjusted to each eye separately (Miller, 1985*a*). Hence pre-motor control of LP is at least partially lateralized, though the motor nucleus (CCN) is unpaired. The phylogenetically old condition, where LP was innervated by contralateral neurons, may thus be partially retained at the pre-motor level.

Modulation of tonic LP motor neuronal activity

Inhibitory modulation of a basal LP tonus appears to be involved in many eyelid functions, i.e. in blinking, lid-eye coordination, voluntary lid closure and possibly in LP relaxation during sleep. The generator for tonic CCN activity is unknown. The close relationship of lid position with the level of arousal indicates that CCN receives corresponding unspecific afferences. Since palsy of LP occurs only in damage to CCN or close to it, a hypothetical motor neuronal tonus generator has to be assumed within or in close vicinity to CCN. Several lines of evidence point to a role of the ventral PAG overlying CCN. Among other sources, the PAG receives afferents from the limbic system and reticular formation, and is involved in functions intimately related to the level of arousal (e.g. rage reactions, vocalization, pain; Brodal, 1981). In rabbits and guinea pigs, each OMN motor neuron was shown to send at least one dendrite into the PAG and the 'supraoculomotor area' dorsal to the OMN (Evinger *et al.*, 1987; Evinger, 1988). Electrical stimulation of the PAG dorsal to CCN evokes lid retraction in anaesthetized monkeys (personal observation). In two human patients, electrical stimulation close to the aqueduct, on levels from below CCN to the superior colliculus, induced ipsi- and bilateral lid retraction (Nashold and Gills, 1967). Destruction of the PAG may have been the cause of ptosis in the case of a periaqueductally spreading

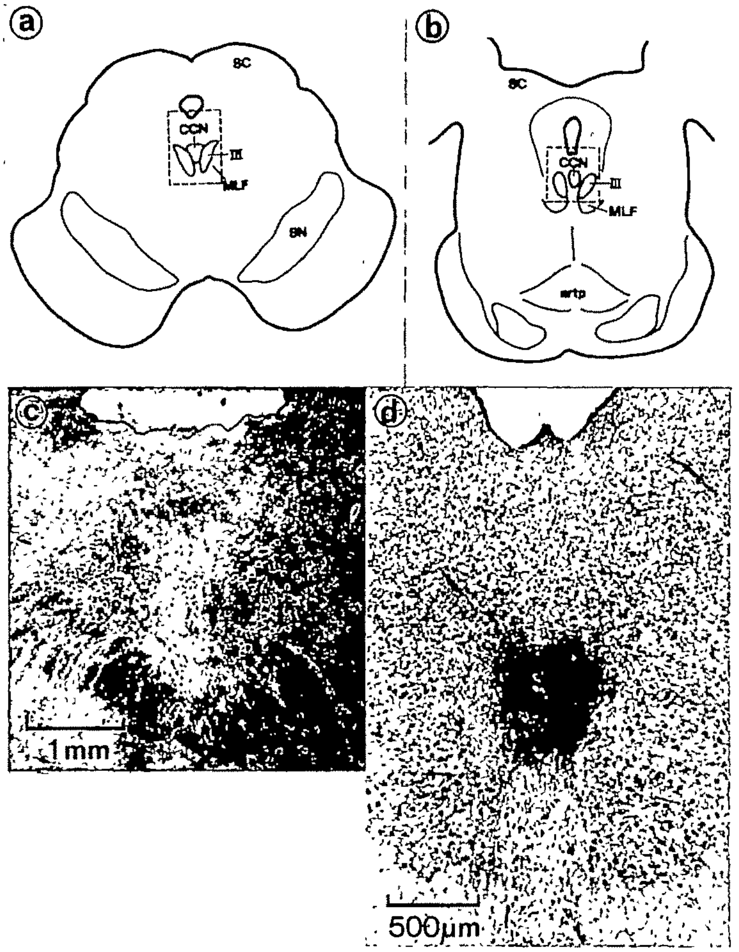

FIG 2. Drawing of the human brainstem (*a*, transverse section) and the monkey brainstem (*b*, frontal section) at the level of the caudal oculomotor nucleus, including the central caudal nucleus which contains the levator palpebrae motor neurons. Insets refer to the subajacent photographs. Abbreviations: III = oculomotor nucleus, CCN = central caudal nucleus; MLF = medial longitudinal fasciculus, nrtp = nucleus reticularis tegmentum pontis; SC = superior colliculus; SN = substantia nigra. *c*, Nissl stained section through the caudal oculomotor nucleus in man. The levator palpebrae motor neurons in the central caudal nucleus lie around the midline. See overlying graphic for location. *d*, Nissl counter-stained section through the caudal oculomotor nucleus in the macaque monkey. Radioactive wheatgerm agglutinin was previously injected into the levator palpebrae muscle on the right side. After retrograde transport into the motor neurons the tracer was visualized by standard autoradiographic techniques The levator palpebrae motor neurons lie bilaterally in the central caudal nucleus and appear black, covered with silver grains. See overlying graphic for location.

metastasis (Stevenson and Hoyt, 1963). Marked asymmetrical ptosis was also present in another patient with a periaqueductally spreading astrocytoma that had infiltrated and destroyed large parts of the PAG, while the majority of CCN neurons remained intact (Büttner-Ennever *et al.*, 1989).

Lid-eye coordination

Vertical globe movements are based on the cooperation of systems for upgaze and for downgaze that are separate on the muscular motor neuronal, and probably on the

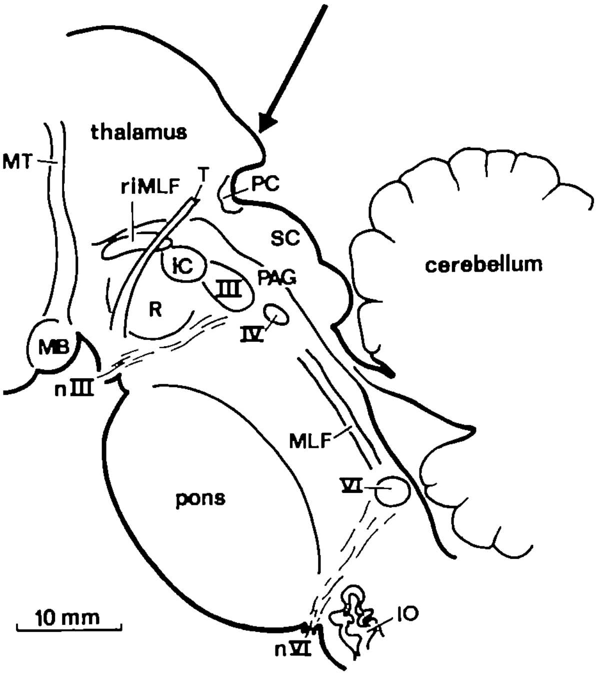

FIG. 3. A drawing of a sagittal section through the human brainstem, to show some of the structures discussed in connection with the motor and pre-motor control of the eyelid. Abbreviations as in FIG. 4.

pre-motor level. The mesencephalic rostral interstitial nucleus of the MLF (riMLF, *see* Fig. 3) is the principal pre-motor structure for the generation of voluntary saccades in both vertical directions (Büttner-Ennever and Büttner, 1978; Büttner-Ennever *et al.*, 1982). The pre-motor areas controlling smooth pursuit movements are less clear. If lesions to the area of the riMLF are bilateral, saccadic vertical gaze is abolished. Clinico-pathological and experimental studies suggest that slightly different lesions are responsible for up- versus downgaze paralysis (Kömpf *et al.*, 1979; Büttner-Ennever *et al.*, 1982). Only those efferences that induce upgaze saccades are thought to cross in the PC (Pierrot-Deseilligny *et al.*, 1982). Accordingly, selective upgaze paralysis is observed in lesions that destroy (1) portions of the riMLF and/or (2) the PC and its fibres (dorsal midbrain syndrome). In contrast, selective downgaze paralysis is only seen in circumscribed and symmetric lesions to certain parts of the riMLF (an exception is the case of André-Thomas *et al.*, 1933).

The linkage between vertical eye and lid movements is very tight in normal and pathological conditions. Independent lid movements are an extreme rarity, and isolated defects of lid-eye coordination (lid lag) have never been reported in circumscribed lesions. The precision of lid-eye coordination and the fact that LP is derived developmentally from superior rectus, leave little doubt that pre-motor saccadic signals to LP and the vertical eye muscles come from a common source. Evidence exists that signals for both up- and downgaze contribute to the control of LP: in conjugate gaze paralysis to just one vertical direction, the lids remain coupled to saccades in the intact direction, and also to pursuit and reflexive eye movements in the disturbed direction, where present (e.g. Schuster, 1921, case 1). Furthermore, the lids can retain the ability to perform appropriate movements upon attempted saccades to the disturbed vertical direction. Particularly, they often remain able to lower in selective paralysis of downgaze, leading to pseudoptosis upon attempted downgaze (André-Thomas *et al.*, 1933; Cogan, 1974; Trojanowski and Wray, 1980; LoBue and Feldon, 1983). The analogous sign of lids elevating upon attempted upgaze in upgaze paralysis has been described (Spiller, 1905, case 4; Orzechowski, 1933, case 1; Christoff *et al.*, 1960; Balthasar and Hopf, 1966; Cogan, 1974), and should appropriately be termed (neurogenic) pseudoretraction.

Lid retraction—experimental lesion studies

Bilateral transient lid retraction was evoked in three of eight human patients who underwent unilateral stereotactic lesions close to the PC for relief of chronic pain (Nashold and Gills, 1967). In a later series with lesions at the level of the superior colliculi, close to the PC but apparently sparing it and its nuclei, lid retraction was not noted, while vertical gaze paralysis and convergence deficit were again present (Nashold and Seaber, 1972). Pathological lid signs were also absent when the lesions were placed 5 mm further caudally (Seaber and Nashold, 1980).

Following destruction of the monkey PC, Carpenter *et al.* (1970) observed strong bilateral lid retraction, upgaze paralysis and other ocular deficits. The same syndrome was noted upon lesions to the medial pretectal area that involved the PC or led to degeneration of PC fibres (Bender and Shanzer, 1964; Pasik *et al.*, 1966). Following lesions of PC or nPC (nuclei of the PC) the development of a Parinaud's syndrome, including upgaze paralysis, lid lag and some degree of lid retraction was noted (Pasik *et al.*, 1969*a*; Pasik and Pasik, 1975). Transient marked lid retraction and lid lag were seen after a unilateral lesion to ventral PC fibres and intermixed neurons of the nPC (Carpenter *et al.*, 1970). Mild post-operative lid retraction was observed following lesions dorsolateral to the interstitial nucleus of Cajal (iC) which destroyed ventrally located nPC neurons, and following lesions to the nucleus of Darkschewitsch and the lateral PAG that involved fibre pathways crossing in the PC. Lid retraction never occurred in monkeys with lesions to iC (Carpenter *et al.*, 1970; Fukushima 1987), to superior colliculi (Pasik *et al.*, 1966), and when PC and nPC were completely spared. In cats, no lid anomalies were noted following pretectal- and PC-lesions (Szentágothai, 1942*b*). However, cats (and dogs) show very poor lid-eye coordination (personal observation).

Lid retraction—clinico-pathological lesion studies

In order to determine the critical structure for lid retraction in humans more precisely, we searched the literature for clinico-pathological reports of human lid retraction cases. Only a few studies report both lid symptoms and post-mortem findings; the following cases were found to be sufficiently detailed to be used here: Collier, case 1 (1927), André-Thomas *et al.* (1933), Hatcher and Klintworth (1966) and Pierrot-Deseilligny *et al.*, case 3 (1982). Except for a haemorrhage in Collier's case, all lesions were of ischaemic origin. All cases exhibited marked lid retraction. Additional upgaze paralysis was present in three cases, selective downgaze paralysis in the case of André-Thomas *et al.* (1933). The outlines of the lesioned zones were transferred onto a set of four

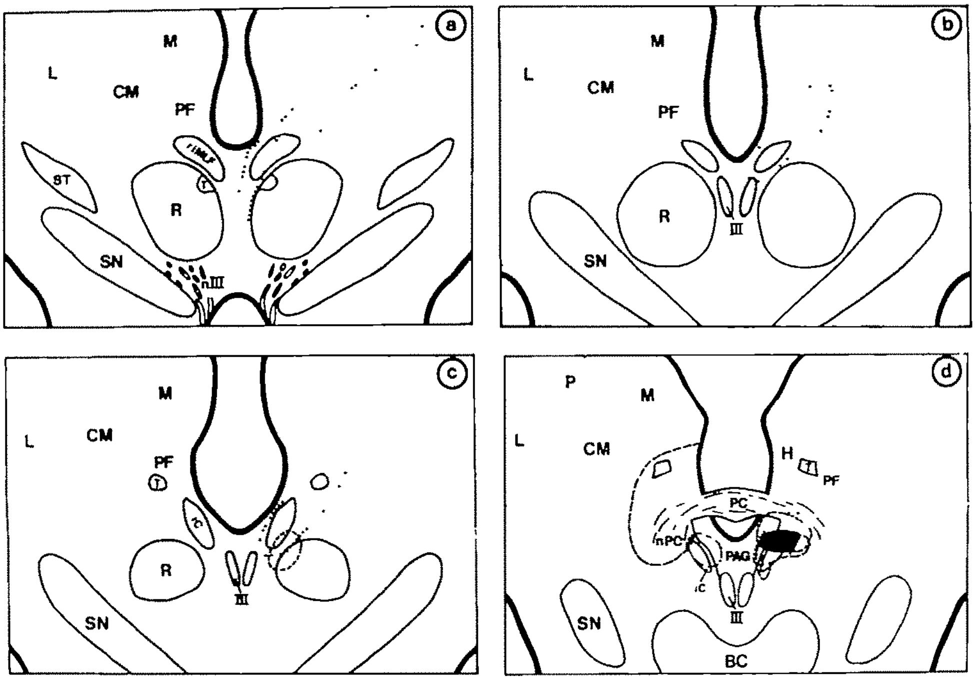

FIG. 4. Lesion zones in four human cases *with lid retraction* and vertical gaze paralysis. *a–d* is rostral to caudal Distance between sections is approximately 2 mm The shaded area denotes the common area involved in all four cases; it lies in the nPC. · · · · · · Pierrot-Deseilligny *et al*, case 3 (1982), — — — — — — Hatcher and Klintworth (1966); — — — — — — Collier (1927); — · — · — · André-Thomas *et al* (1933) Abbreviations: BC = brachium conjunctivum; CM = nucleus centralis medialis thalami; iC = interstitial nucleus of Cajal; H = habenular nuclei, IO = inferior olive; L = lateral thalamic nuclei; M = nucleus medialis dorsalis thalami; nPC = nuclei of the posterior commissure; nIII = oculomotor nerve; nVI = abducens nerve; PAG = periaqueductal grey; MB = mamillary body, MLF = medial longitudinal fasciculus, MT = mamillothalamic tract; PC = posterior commissure; PF = nucleus parafascicularis thalami; R = nucleus ruber; riMLF = rostral interstitial nucleus of the medial longitudinal fasciculus; SC = superior colliculus, SN = substantia nigra; ST = nucleus subthalamicus; T = tractus retroflexus; III = oculomotor nucleus; IV = trochlear nucleus, VI = abducens nucleus.

representative drawings of the midbrain (Fig. 4), in order to show the common-lesion area (Fig. 4*d*, shaded black). In the four cases *with lid retraction* plus vertical gaze paralysis, the lesion zones are concentrated around the nPC. The common lesion zone of all cases covers a portion of the laterally spreading PC fibres and comprises the embedded principal and magnocellular portion of the nPC (Carpenter and Peter, 1970).

Four further cases of vertical gaze paralysis *without lid retraction* were selected as a control: Molnár (1959), Balthasar and Hopf (1966), Pierrot-Deseilligny *et al.*, case 5 (1982) and Büttner-Ennever *et al.* (1982). The first three cases had upgaze paralysis. The last case had complete vertical gaze paralysis; the original sections were available for inspection. The borders of these lesions were also reconstructed onto the same set of midbrain drawings (Fig. 5). In these control cases (vertical gaze paralysis without lid retraction), the lesions are concentrated more rostrally, involving the riMLF and iC. Parts of the PAG are destroyed in two cases (Fig. 5*d*). The nuclei and fibres of the PC are spared in all cases.

The comparison of cases with and without lid retraction (Fig. 4 vs Fig. 5) suggests that a unilateral lesion to the nPC produces the lid deficits. The common-lesion area does not spread into the PC itself, therefore it is likely that the neurons of nPC region, and perhaps also fibres of passage, are crucial for the lid retraction. Observations of lid retraction following damage to the PC proper could be explained by the strong interconnection of the nPC of each side via the PC.

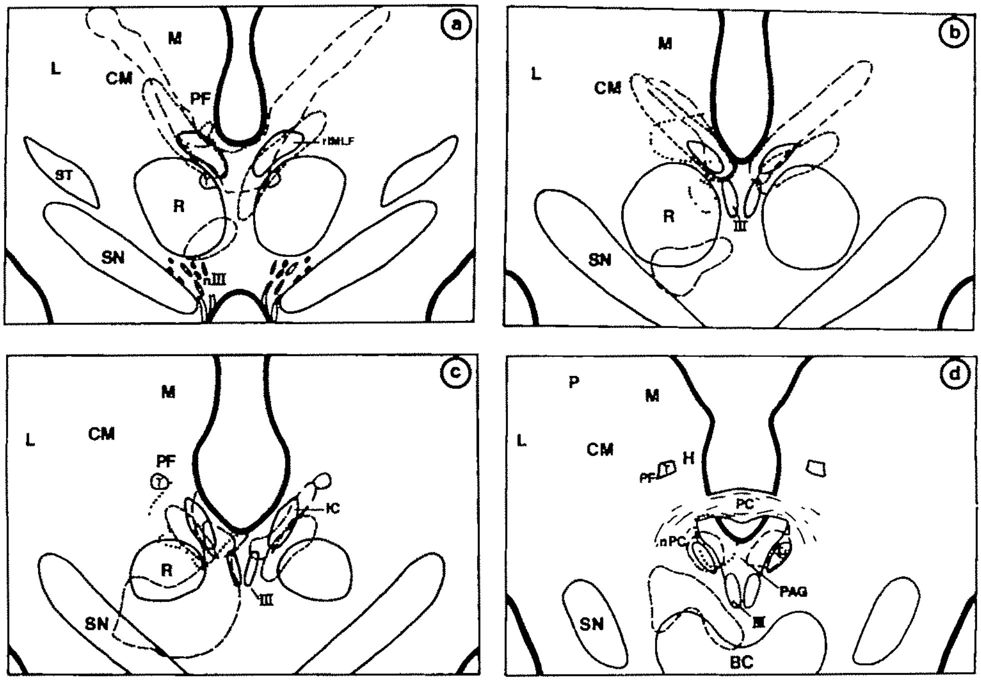

FIG. 5. Lesion zones in four human control cases with vertical gaze paralysis but *without lid retraction*. Abbreviations as in FIG. 4 Note the minimum involvement of the nPC in comparison with FIG. 4. · · · · · · Balthasar and Hopf (1966); – – – – – – Buttner-Ennever *et al.* (1982), —————— Molnár (1959); — · — · — · Pierrot-Deseilligny *et al* , case 5 (1982).

Pre-motor control of the eyelids: conclusions

No direct evidence on the pre-motor network controlling levator motor neurons has been published yet; however, there are several indications as to some structures which may be involved. From the evidence accounted in the section Nervous control of eyelid function: lid-eye coordination, it follows that the riMLF is likely to be involved in the control of LP in saccadic vertical gaze changes. In our studies of the iC (*see* Fig. 3) and riMLF (Kömpf *et al.*, 1979; Büttner-Ennever *et al.*, 1982; Pierrot-Deseilligny *et al.*, 1982; Büttner-Ennever and Büttner, 1988), we have seen direct projections from these areas to the levator motor neuron pool (Büttner-Ennever, 1981, Fig. 3D, and unpublished results). However, the precise mechanism and pathways are unclear.

There is indirect evidence that, additional to vertical gaze structures, the control of LP in lid-eye coordination involves further, interposed pre-motor structures: (1) patients with degenerative extrapyramidal disease, namely parkinsonism, can show lid lag, the isolated disturbance of lid-eye coordination, while vertical gaze is intact (Duke-Elder and Scott, 1971; Miller, 1985*b*); (2) lid position in normal persons can undergo minor spontaneous shifts while the globes stand still fixating a target; (3) the positions taken by the lids at the end of identical gaze changes may vary considerably (Becker and Fuchs, 1988).

Converging evidence on the phenomenon of lid retraction, provided by clinical and animal studies (*see above* Nervous control of eyelid function: lid retraction—experimental lesion studies) and by our analysis of clinico-pathological lesion studies (*see above* Nervous control of eyelid function: clinico-pathological lesion studies) indicates a role of the nuclear complex of the PC in pre-motor lid control. Support is also provided by the observation of modest scattering degeneration of LP motor neurons after bilateral destruction of the critical nPC area (Carpenter *et al.*, 1970). The fact that lesions to the nPC, in particular its magnocellular subdivision, or damage to PC fibres result in bilateral lid retraction implies a connection between nPC and LP motor neurons, which appears to be inhibitory. In this context, it is of interest that IPSPs were found to be evoked in motor neurons of a vertical eye muscle (inferior rectus) by stimulation of the nPC (Grantyn *et al.*, 1982).

No direct projections from nPC to the OMN have been shown, but there are some reports of projections from nPC to an area directly overlying the OMN (Grantyn, 1988; for a review of nPC connectivity, *see* Büttner-Ennever and Büttner, 1988). All LP motor neurons are multipolar and send dendrites into this region of the PAG, called here the supraoculomotor area (SOA) (May and Baker, 1987; Evinger, 1988). LP dendrites may thus well have access to inputs from the nPC, as well as from many limbic inputs known to relay in the PAG (Baskin *et al.*, 1986; Tan and Holstege, 1986). Several other structures known to be involved in the pre-motor control of eye movements also relay within the SOA: the superior colliculus (Edwards and Henkel, 1978; Huerta and Harting, 1984), the sensory trigeminal nucleus (May *et al.*, 1984; McHaffie *et al.*, 1986) and putative pontine and medullary pre-motor blink areas (Holstege *et al.*, 1986). Electrophysiological investigation of LP motor neurons provided evidence for a slow, monosynaptic inhibitory input from neurons within the SOA (May, personal communication). The SOA is a rather loose term, which certainly includes several projection fields; however, the main point to be emphasized here is that it is a possible site for pre-motor interactions of signals controlling LP motor neurons.

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STRONG IMMUNOREACTIVITY OF CATHEPSIN L AT THE SITE OF RIMMED VACUOLES IN DISEASED MUSCLES

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SUMMARY

Skeletal muscle samples from four patients with myopathies showing autophagic vacuole formation were examined by immunohistochemical, biochemical and immunoblot analyses. Immunochemical studies demonstrated strongly positive reactions of cathepsins B and L in and around the rimmed vacuoles and weak reactions in intramyofibral portions of degenerating muscle fibres. Faint staining of cathepsin H was also seen at the sites of rimmed vacuoles. Biochemical analyses showed increased activity of cathepsin B and L in muscle specimens from the patients with rimmed vacuole formation. However, there was no remarkable cathepsin H activity in the muscle specimens from these patients. Cathepsin L immunoblot analysis of muscle extracts showed three bands with molecular masses of 30 kDa, 36 kDa and 39 kDa. The immunostaining of cathepsin L from patients with rimmed vacuole formation was stronger than that of normal controls. Cathepsin B immunoblot analysis showed only faint bands in samples from patients with rimmed vacuole formation and normal controls. This study demonstrated, for the first time, strong immunoreactivity of cathepsin L at the sites of rimmed vacuoles. Possible mechanisms of rimmed vacuole formation are discussed.

INTRODUCTION

Lyosomal systems are important in cellular metabolism and degradation. Mature skeletal muscle fibres have poorly developed lysosomal systems, but the number of lysosomes increases in pathological and some physiological conditions. For example, immature developing muscle cells and regenerating muscle cells contain well-developed lysosomal systems (Wakayama *et al.*, 1984). In pathological skeletal muscles, the ultrastructure of muscle fibres with rimmed vacuole formation have numerous secondary lysosomes such as myelin figures (Nonaka *et al.*, 1981; Kumamoto *et al.*, 1982). Immunohistochemical investigation by Ii *et al.* (1986) has demonstrated that proteinases in the muscle fibres increased in one case of distal myopathy with rimmed vacuoles, and suggested that autodigestion by intramyofibral lysosomal proteinases was responsible for rimmed vacuole formation. We report here, from immunohistochemical and biochemical analyses, increased amounts of lysosomal proteinases in two cases of distal myopathy with rimmed vacuoles, one case of inclusion body myositis, and one case of undiagnosed myopathy associated with rimmed vacuoles.

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CASE REPORTS

Case 1

A 23-yr-old woman was well until her 17th year, when she noticed leg heaviness when she ran or jumped. This gradually became worse, until at age 23 yrs it became difficult for her to walk without a cane. At this time she presented herself at the Showa University Hospital. There was no family history of similar muscle disorders. Neurological examination revealed no cranial nerve abnormalities. Deep tendon reflexes in all four limbs were moderately hypoactive, especially in the legs, and there were no pathological reflexes. There was distal dominant muscle weakness and moderate atrophy. There were no other neurological abnormalities. Laboratory findings showed a moderately elevated serum creatine kinase (CK) value of 2.9 times the control level and a myopathic electromyogram (EMG) pattern. Muscle CT scan revealed widespread low density areas in the distal muscles of all four limbs.

Muscle biopsy was taken from the quadriceps femoris muscle. Standard histological and histochemical examinations of biopsied muscle, including haematoxylin-eosin (HE), Gomori-trichrome (GT), nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR), periodic acid Schiff (PAS) and myosin adenosine triphosphatase (ATPase) (pH 9.4, 4.6, 4.3) stains, were performed on frozen sections. Findings included moderate variation of fibre size, mild infiltrations of connective tissue, scattered small angulated muscle fibres and rimmed vacuoles, predominantly in small calibred muscle fibres. The vacuoles were rimmed by basophilic material with the HE stain and by metachromatic material with the GT stain, and tended to be present in type 1 muscle fibres as judged by the myosin ATPase stain. The shape of the vacuoles was round, oval or slit-like. They occurred in 12% of 200 muscle fibres. No infiltration of inflammatory mononuclear cells was noted. Neither fibre type grouping nor grouping of atrophic fibres were revealed by the myosin ATPase stain. Necrotic or regenerating muscle fibres were rarely observed. Electron microscopy showed numerous myeloid bodies in the rimmed vacuoles, but no filamentous inclusion was observed in the vacuoles or nuclei. The diagnosis was distal myopathy with rimmed vacuoles.

Case 2

A 22-yr-old man visited our hospital complaining of a 1 yr history of muscular wasting in both legs. There was no family history of similar muscle disorders. Physical examination showed the operative scar for repair of cleft lip and primary cleft palate. Neurological examination disclosed nasal voice of mild degree, a slightly diminished gag reflex, moderate atrophy of both legs, and mild weakness of dorsiflexion of the feet, more marked on the right side. Sensation was intact. Laboratory investigations showed serum CK value elevated to 3.9 times the control level, and a myopathic EMG pattern without myotonic discharge. Muscle CT scan results were normal in the thighs, but there was evidence of atrophy and a moth-eaten appearance in the extensors and flexors of both legs.

Standard histological and histochemical examination of frozen sections of the biopsied right gastrocnemius muscle revealed moderate variation of fibre size, mild connective tissue infiltration and scattered rimmed vacuoles, the characteristics of which were similar to those observed in Case 1. There were rimmed vacuoles in 9% of the muscle fibres. There was no evidence of infiltration of inflammatory mononuclear cells or necrotic fibres. On myosin ATPase staining, no fibre type grouping was seen. Electron microscopy of the vacuolated fibres showed the presence of numerous myeloid bodies and some membrane bound glycogen granules in and around the vacuoles.

No filamentous inclusion was found. No Golgi apparatus was noted in and around the vacuoles. The diagnosis was distal myopathy with rimmed vacuoles.

Case 3

A 72-yr-old man visited our hospital with muscle weakness which had developed during the previous 2 yrs. A family history of similar muscle disorders was not present. The results of physical examination were normal. Neurological examination revealed normal cranial nerve functions and severely hypoactive deep tendon reflexes in all four limbs. There was mild to moderate proximal muscle atrophy and weakness in all four limbs. Gowers' sign was positive. Sensation was intact and there was no fasciculation. Laboratory findings included a serum CK value of 2.0 times the control level, and a myopathic EMG pattern. Nerve conduction velocities were normal. No findings of inflammatory reaction, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were noted in the laboratory data. Muscle CT scan revealed atrophy and reduced density of the thighs, more marked in the extensors, but CT scan of the distal muscles appeared normal.

Standard light microscopic examination of frozen sections of the biopsied right quadriceps femoris muscle showed marked variation of fibre size, moderate connective tissue infiltration and abundant rimmed vacuoles which had characteristics similar to those of Cases 1 and 2 (Fig. 1A,B). There were vacuoles in 22% of the muscle fibres. Mild infiltrations of endomysial inflammatory mononuclear cells were observed. Necrotic or regenerating muscle fibres were rare. On myosin ATPase staining, mild predominance of type 1 fibres and type 2 atrophy were seen. Electron microscopic examination revealed numerous myeloid bodies in and around the vacuoles. There were 15–20 nm diameter intracytoplasmic filamentous inclusions near the vacuoles. No intranuclear inclusions were seen. He was treated with predonisone at a dose of 60 mg daily for 2 wks. He was diagnosed as having inclusion body myositis

Case 4

A 64-yr-old woman presented with difficulty in rising from a sitting position, which she had noticed since aged 60 yrs. At around 50 yrs, she had suffered from gradually worsening low back pain and heaviness of the left lower limb. There was no family history of muscle disorder. Her cranial nerve function was normal and the deep tendon reflexes of all four limbs were slightly hyperactive except for the achilles jerks which were absent. There was diffuse muscle atrophy of all four limbs with mild to moderate muscle weakness. She had a waddling gait and a positive Gowers' sign. Sensation was intact. Laboratory findings included serum CK values, raised 3.0 times the control level and a myopathic EMG pattern. Muscle CT scan revealed abnormal low density areas in the paravertebral muscles, flexor muscles of the thighs and both extensor and flexor muscles of the legs, more marked in the left side.

Standard histological and histochemical examination of frozen sections of the biopsied quadriceps femoris muscle showed moderate variation of fibre size and mild connective tissue proliferation. Rimmed vacuoles were less numerous than in the other cases and there were slit-like vacuoles in only 4% of the muscle fibres.

Intracytoplasmic metachromatic material, which was considered to be the product of degeneration, was revealed in some muscle fibres by GT stain. These fibres were not invaded by macrophages or mononuclear inflammatory cells. No necrotic muscle fibres were encountered. Myosin ATPase staining revealed no abnormality. Electron microscopy showed numerous secondary lysosomes and myeloid bodies in the cytoplasm of degenerating muscle fibre. No filamentous inclusions were observed. The patient was considered to have activated lysosomal proteinases in skeletal muscle fibre, but could not be diagnosed according to the current classification of neuromuscular disorders.

METHODS

Normal and disease control muscle specimens

Histochemically normal control quadriceps femoris muscles were obtained from 12 patients undergoing orthopaedic operations or from patients who had myalgia with minimal weakness and were deemed to be free of neuromuscular diseases after full examination. The age range of the control group was 28–65 yrs (mean 49.8 yrs). Two patients with non-rimmed vacuoles served as disease controls. The first patient (Case 5), a 36-yr-old man, was diagnosed as having hypokalaemic periodic paralysis, and muscle biopsy from the quadriceps femoris muscle revealed mild variation of fibre size and scattered vacuoles. The vacuoles were not rimmed by GT stain and occurred in 4% of the muscle fibres. No necrotic muscle fibres or mononuclear cellular infiltration were observed. Another patient (Case 6), a 58-yr-old man, was diagnosed as having alcoholic hypokalaemic myopathy. The patient, who had a long history of severe alcoholism, developed muscle weakness that lasted a week during which time severe hypokalaemia (serum K 1.7 mEq/l) was present. Laboratory tests revealed serum CK level at 49.8 times the control. Biopsy of quadriceps femoris muscle showed moderate variation of fibre size, moderate infiltration of connective tissue and vacuoles. Multiple vacuoles were seen within a single muscle fibre, but no vacuole was rimmed by GT stain. The vacuoles occurred in 6% of the muscle fibres. There were scattered necrotic myofibres undergoing phagocytosis. Moderate infiltration of inflammatory mononuclear cells, including macrophages, was observed in the endomysial space and in muscle fibres with phagocytosis.

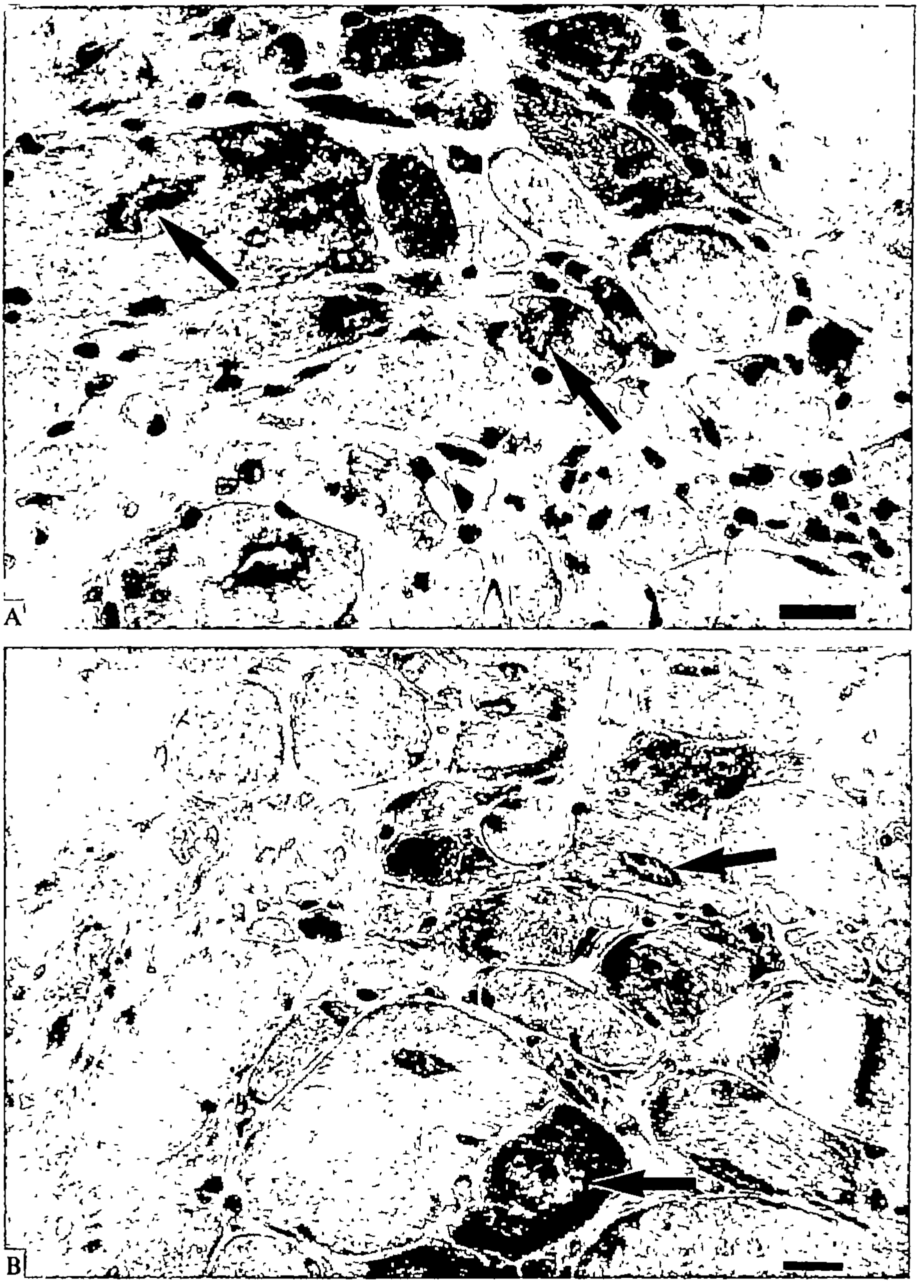

FIG. 1. A, scattered rimmed vacuoles (arrows), which tend to be present in atrophic myofibres. Haematoxylin-eosin stain. Bar = 20 μm (Case 3). B, rimmed vacuoles (arrows). Gomori-Trichrome stain. Bar = 30 μm (Case 3)

Purification of human liver cathepsins B, H and L

Human cathepsins B and H, and cathepsin L were purified from liver obtained at autopsy according to the methods of Schwartz and Barrett (1980) and Mason *et al.* (1985), respectively, with minor modifications. Fractions of each cathepsin were specifically separated by chromatography on a CM-Sephadex C-50 column. Cathepsins B and H were eluted with a linear gradient of 0 to 0.25 M NaCl in 20 mM acetate buffer, pH 5.5, containing 1 mM EDTA, and then cathepsin L was eluted with 0.45 M NaCl in the same buffer by stepwise elution. The final preparations were apparently homogenous on SDS-PAGE although they sometimes showed double bands, as reported previously by Mason *et al.* (1985).

Preparation of anti-human cathepsin B, H and L sera

Rabbit antisera against human cathepsins B, H and L were produced by immunizing three rabbits, each with 250 μg of antigen emulsified with an equal volume of complete Freund's adjuvant, and then injected intradermally. Additional booster injections were administered 3 wks after immunization and followed four times at 1 wk intervals. Each rabbit was bled 1 wk after the final injection. The IgG fraction from the antiserum was isolated by fractionation with ammonium sulphate and purified by affinity chromatography on a cathepsin-Sepharose 4B column. Anticathepsins B, H and L IgG were conjugated with horseradish peroxidase (HRP) according to the method of Nakane and Kawaoi (1974). Solid phase enzyme-linked immunosorbent assay was used to determine the antibody titres, which were 8000, 3200 and 4000 for cathepsins B, H and L, respectively.

Immunohistochemistry

Usually, the muscle with rimmed vacuoles and control muscles were placed on the same glass slide in 7 μm thick serial frozen sections. These samples were immersed in 0.3% H_2O_2 in absolute methanol for 30 min at room temperature to block endogenous peroxidase activity. The sections were then incubated for 20 min at room temperature with 5% normal rabbit serum diluted in phosphate buffered saline (PBS) to eliminate non-specific reactions. After washing three times in PBS, they were incubated overnight at 4°C with anticathepsins B, H and L IgG-HRP conjugates diluted 1 : 20 in PBS and washed three times in PBS. Then the sections were stained with 0.04% 3,3'-diaminobenzidine tetrahydrochloride (DAB) plus 0.01% H_2O_2 in PBS for 4 min at room temperature, washed with PBS, counterstained with haematoxylin for 10 s, dehydrated, cleared and mounted.

Some immuno-control samples were analysed. Pre-immune rabbit serum or antibody against other antigens such as anti-mouse immunoglobulin rabbit serum were used instead of primary anti-cathepsin antibodies for negative immuno-controls. The blocking test was carried out as a control to ascertain the reduction in immunoreactivity produced by pre-incubation with non-labelled anti-cathepsin antibody before applying labelled antibody. Some consecutive sections were stained without counterstaining with haematoxylin to eliminate possible enhancement by the haematoxylin.

Biochemistry

The stored muscle samples were homogenized and portions of the supernatant were used for assay. The activities of cathepsins B, B and L, and H were measured by a modified method of Barrett and Kirschke (1981) using the synthetic substrates, Z-Arg-Arg-MCA, Z-Phe-Arg-MCA and Arg-MCA, respectively (Z = benzoyloxycarbonyl; MCA = methyl coumanin). Activity of cysteine proteinase inhibitor was measured according to the method of Kominami *et al.* (1982) with minor modifications. Activities of acid phosphatase (Igarashi and Hollander, 1968) and β-D-glucosidase (Daniels and Glew, 1984) were measured by the methods reported previously.

Immunoblotting

For immunoblot analyses of cathepsins B and L, the supernatant of the homogenates was treated by adding an equal volume of 0.1 M Tris-HCl buffer, pH 8.0, containing 10% SDS, 10 mM EDTA, 1% 2-mercaptoethanol and 10% glycerol, and then boiling for 1 min in a water bath. After removing insoluble material by centrifugation, the supernatant was subjected to SDS-PAGE according to Laemmli's method (Laemmli, 1970) using a 12.5% gel (w/v). Proteins were transferred from the gel to a Clearblot P membrane (ATTO Co., Japan) by horizontal electrophoresis according to the method of Towbin *et al.* (1979). Immunostaining with rabbit antiserum was performed using the Promega protocol with alkaline phosphatase conjugated goat anti-rabbit secondary antibody (Promega Biotec., USA).

RESULTS

Immunohistochemistry

Standard light and electron microscopic and immunohistochemical findings from the four patients with rimmed vacuoles are summarized in Table 1. Immunohistochemical study using antibodies against human cathepsins B and L demonstrated positive immunoreaction in and around the rimmed vacuoles of the muscle fibres. Most of these were present in degenerating and atrophic muscle fibres (Fig. 2A,C). Immunoreactions of cathepsin L were stronger than those of cathepsin B. In addition, weak reactions of cathepsins B and L were observed occasionally in portions of degenerating muscle fibres. In the muscle fibres of Case 4, positive immunoreactions of cathepsins B, H and L were observed in the portions in which metachromatic material with the GT stain were present. In contrast, the weak or faint immunoreactions of cathepsin H were noted at the sites of vacuoles, in most cases (Fig. 2B). No immunoreactions were present in the sarcoplasm of apparently normal muscle fibres in any case. No immunoreaction was noted in or around the intrasarcoplasmic vacuoles of two disease control muscles (Cases 5, 6) with cathepsins B, H and L antibodies (Fig. 3). However, positive immunoreactions of cathepsin B was observed in the infiltrating mononuclear cells especially in macrophages of the muscle sample of Case 6. Negative immuno-controls, which substitute primary anti-cathepsin antibodies for pre-immune serum or antibody against other immunogens, gave no reactions in or around the rimmed vacuoles. Remarkably reduced immunostainability was observed with each antibody by the blocking test. Samples without counterstaining by haematoxylin revealed similar immunostainability with each antibody. Samples from normal controls revealed no immunoreactions.

TABLE 1 SUMMARY OF HISTOLOGY, HISTOCHEMISTRY, ELECTRON MICROSCOPY AND IMMUNOCHEMISTRY

		Histology and histochemistry				*Immunohistochemistry*		
Case	*Diagnosis*	*Rimmed vacuole*	*Cellular infiltration*	*Neurogenic pattern*	*Electron microscopy*	*Cathepsin B*	*Cathepsin H*	*Cathepsin L*
1	DMRV	12%	–	±	MB: +++ GA. –	+ ~ ++	n.d.	n.d
2	DMRV	9%	–	–	MB: +++ GA: –	+ ~ ++	± ~ +	++
3	IBM	22%	+	±	MB: +++ GA: –	++	± ~ +	+++
4	MRV	4%	–	–	MB +++ GA: –	+ ~ ++	± ~ +	++

DMRV = distal myopathy with rimmed vacuoles; IBM = inclusion body myositis; MRV = myopathy associated with rimmed vacuole formation; MB = myeloid body; GA = Golgi apparatus, n.d = not done +++ = marked or strong, ++ = moderate, + = mild or weak, ± = minimal or faint

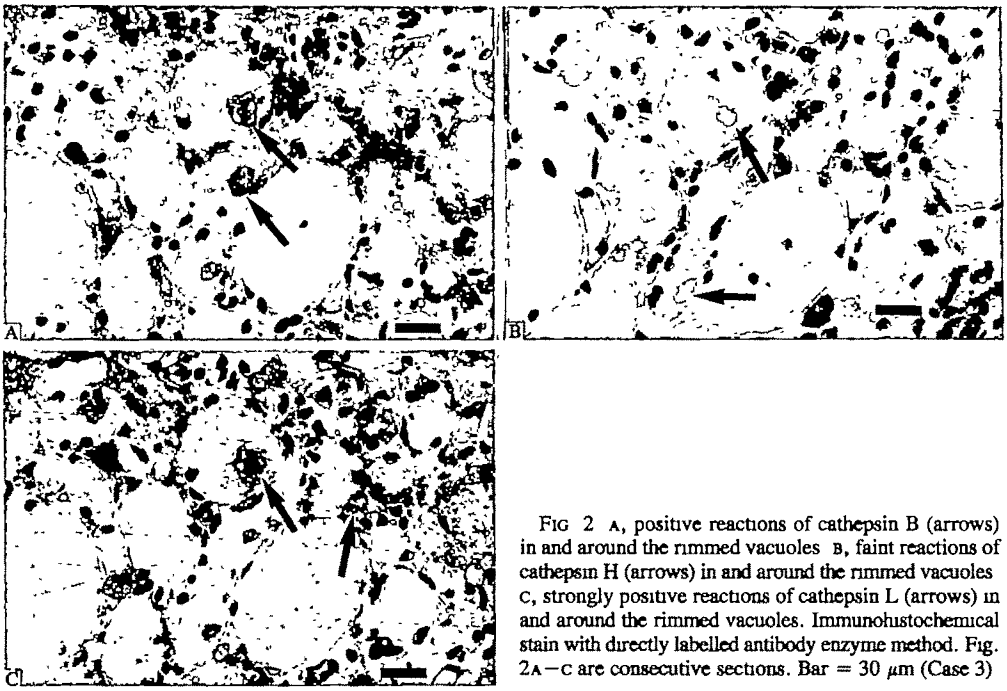

Fig 2 A, positive reactions of cathepsin B (arrows) in and around the rimmed vacuoles B, faint reactions of cathepsin H (arrows) in and around the rimmed vacuoles C, strongly positive reactions of cathepsin L (arrows) in and around the rimmed vacuoles. Immunohistochemical stain with directly labelled antibody enzyme method. Fig. 2A–C are consecutive sections. Bar = 30 μm (Case 3)

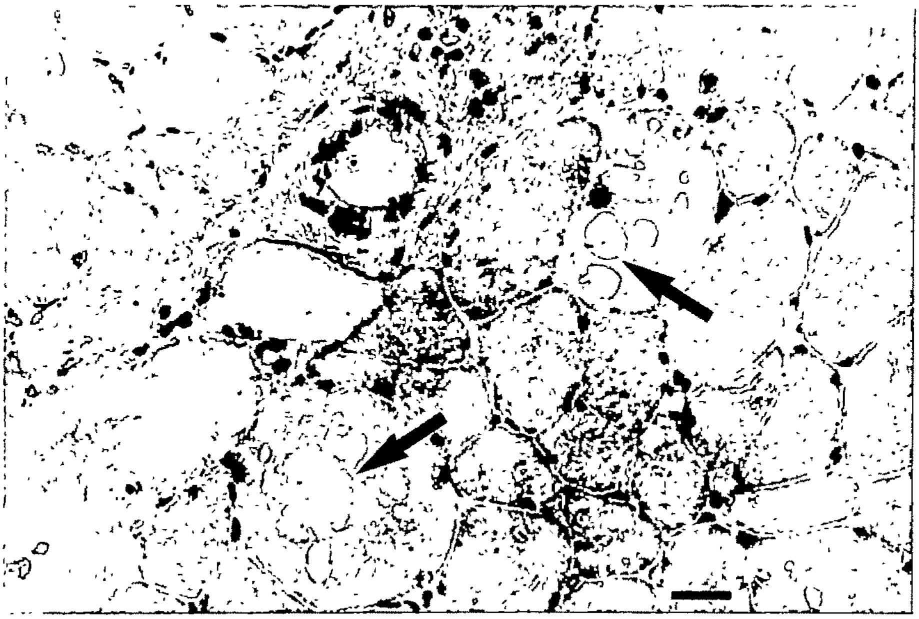

Fig. 3. No immunoreaction is observed at vacuoles that are not rimmed (arrows) Immunohistochemical stain with directly labelled cathepsin L antibody. Bar = 30 μm (Case 6)

Biochemical analyses

Biochemical analyses from four patients with rimmed vacuole, two disease controls and normal controls are summarized in Table 2. The higher cathepsins B and B and L levels were scored in all muscle samples from the four patients with rimmed vacuoles and compared with those from normal controls. The values of cathepsin H of patients were lower than those of normal controls.

The group mean activity levels of cathepsins B, B and L, and H in the muscles of normal controls were 1.21 nmol/min/mg protein, 1.76 nmol/min/mg protein, and 15.17 nmol/min/mg protein, respectively. Their levels of activity in the four patients were 2.96 nmol/min/mg protein, 5.07 nmol/min/mg protein and 11.46 nmol/min/mg protein, respectively. The difference in cathepsin B ($P < 0.05$) and cathepsin B and L ($P < 0.01$) levels between normal controls and patients was statistically significant by the Wilcoxon matched-pairs signed-ranks test. All cathepsin activity in the patient with hypokalaemic periodic paralysis (Case 5) was generally normal, whereas the patient with alcoholic hypokalaemic myopathy (Case 6) had high cathepsin B and B and L values. The cathepsin B activity of Case 6 was the highest of those patients with rimmed and non-rimmed vacuoles. The values of acid phosphatase and β-D-glucosidase in patients with rimmed vacuoles tended to be higher than those of normal controls, but the difference was not statistically significant. The ratios of cathepsin B and L to acid phosphatase and to β-D-glucosidase in patients were significantly higher than those in normal controls. Also, these ratios were higher in patients with rimmed vacuoles than in those with non-rimmed vacuoles.

TABLE 2 SUMMARY OF LYSOSOMAL ENZYME ACTIVITIES

	Cathepsin B	*Cathepsin B and L (A)*	*Cathepsin H*	*CPI*	*AP (B)*	*β-D-Glu (C)*	*$A/B \times 10^3$*	*A/C*
Normal controls (mean ± SD)	1.21 ± 0.57	1.76 ± 0.99	15.17 ± 8.89	17.6 ± 4.8	41.4 ± 5.7	4.6 ± 1.3	42.5	0.38
Case 1	3.50	5.70	7.03	6.5	62.0	6.8	91.9	0.84
Case 2	1.75	4.36	4.50	22.0	56.9	6.3	76.6	0.69
Case 3	2.85	4.42	11.21	23.4	47.7	10.8	92.7	0.41
Case 4	3.73	5.80	23.10	36.8	35.6	5.3	162.9	1.09
Cases 1–4 (mean ± SD)	2.96* ± 0.89	5.07** ± 0.79	11.46 ± 8.24	22.2 ± 12.4	50.6 ± 11.6	7.3 ± 2.4	100.2	0.69
Case 5	1.44	1.52	6.11		56.3	6.7	27.0	0.23
Case 6	5.50	4.69	7.19		79.4	11.5	59.1	0.41

Activities of cathepsins B, B and L, H, cysteine proteinase inhibitor, acid phosphatase, β-D-glucosidase, and the ratios of cathepsin B and L to acid phosphatase and β-D-glucosidase of the muscle specimens from four patients with rimmed vacuoles (Cases 1–4) and two patients with non-rimmed vacuoles (Cases 5, 6) and normal controls. Enzyme activities are expressed as nmol/min/mg protein for cathepsins B, B and L, H, μU/min/mg protein for cysteine proteinase inhibitor, and mU/min/mg protein for acid phosphatase. Enzyme activity of β-D-glucosidase is expressed in arbitrary unit. P values are calculated from Wilcoxon rank sum test. * = $P < 0.05$; ** = $P < 0.01$; CPI = cysteine proteinase inhibitor; AP = acid phosphatase, β-D-glu = β-D-glucosidase.

The group mean levels of activities of cysteine proteinase inhibitor were 17.6 μU/min/mg protein and 22.2/μU/min/mg protein in normal controls and in patients with rimmed vacuoles, respectively. There was no statistically significant difference in cysteine proteinase inhibitor levels between controls and patients by the Wilcoxon matched-pairs signed-ranks test.

Immunoblotting

The presence of cathepsin L in muscle tissues from patients was confirmed by Western blot analysis (Fig. 4). Proteins showing the same molecular masses, 39 kDa and 30 kDa, as cathepsin L of liver tissue were evident in the muscle tissues as well. In addition, the 36 kDa protein which was immunoreactive with anti-cathepsin L antibody was detected in muscle tissues. The staining intensity of the 30 kDa form was stronger than that of the 39 kDa form in the muscle tissue. Cathepsin L in muscle tissue from one patient (Case 3) was especially strongly stained compared with that from normal controls. This was consistent with the immunohistochemical results. Cathepsin B was also detected in muscle tissue from normal controls and patients as a faint band (29 kDa). In muscle tissue of Case 6, immunoreactive strong double bands (29 kDa and 25 kDa), corresponding to the position of a lysosomal form in liver tissue, were detected.

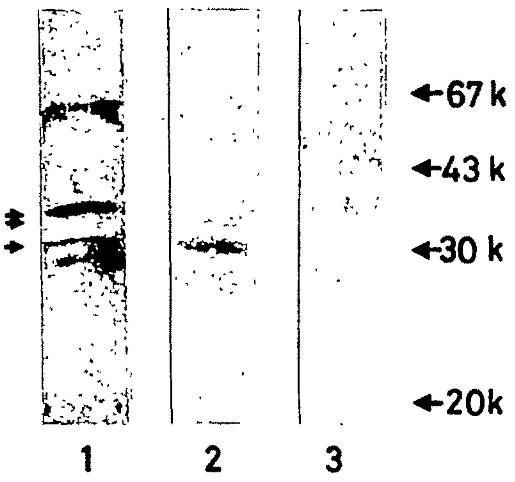

FIG. 4. Immunoblot analysis of cathepsin L in muscle and liver tissues on SDS-PAGE gel Cathepsin L polypeptides are indicated by arrows at the left. The numbers to the right (in kDa) indicate the molecular masses of standards; bovine serum albumin (67 kDa), ovalbumin (43 kDa), carbonic anhydrase (30 kDa) and soybean trypsin inhibitor (20 kDa). (1) Liver microsomal fraction (12 μg) prepared according to the method by Nishimura *et al* (1989); (2) muscle homogenate of Case 3 (48 μg), (3) control muscle homogenate (48 μg)

DISCUSSION

Since the first description of rimmed vacuoles by Dubowitz and Brooke (1973) in oculopharyngeal muscular dystrophy, rimmed vacuoles have been reported in the muscles in a variety of neuromuscular diseases. Although the rimmed vacuole of muscle fibres is a non-specific phenomenon, it is most frequently seen in oculopharyngeal muscular dystrophy, distal myopathy (Nonaka *et al.*, 1981; Kumamoto *et al.*, 1982) and inclusion body myositis (Carpenter *et al.*, 1978). Normal muscle fibres generally contain poorly developed lysosomal systems and until recently, it was not widely accepted that lysosomal proteinases actively participate in the degeneration of muscle fibres. Ii *et al.* (1986) originally reported that abnormal increases of cathepsins B and H were immunohistochemically evident at the sites of rimmed vacuoles and other intramyofibral portions of skeletal muscle fibres obtained from one patient with distal myopathy with rimmed vacuoles. They thought that the focal destruction of muscle fibres and formation of vacuoles was due to autodigestion by these lysosomal proteinases, since they are capable of degrading myofibrillar proteins (Bird *et al.*, 1977; Okitani *et al.*, 1980; Matsukura *et al.*, 1981; Katunuma and Noda, 1982). Sano (1985) reported increased activity of lysosomal enzymes such as cathepsins B and L, D, H, acid phosphatase, α-galactosidase and α-glucosidase in muscle samples of experimental chloroquine myopathy, an experimental model of myopathy with rimmed vacuole formations. Kominami *et al.* (1987) reported that in Duchenne muscular dystrophy, immunoreactions to antibodies of cathepsins B and H were present in the intramyofibral portions of some hyaline (or opaque) muscle fibres as well as in macrophages that invaded and surrounded the necrotic fibres. Nonaka *et al.* (1989) reported biochemically increased level of cathepsin B and L activity in muscle specimens from infants with rapidly progressive nemaline myopathy. These results suggest that autodigestion by intramyofibral lysosomal proteinases is an important event before the digestion of necrotic fibres by invading macrophage proteinases.

In distal myopathy with rimmed vacuoles, infiltration of inflammatory cells has been reported to be generally rare (Nonaka *et al.*, 1981; Kumamoto *et al.* 1982). In our experience reactive cellular infiltration was seldom observed in muscle specimens, except for the patient 3 whose specimen contained mild cellular infiltration. Therefore, the total activities of these proteinases might be minimally affected by infiltrating macrophages in the present study and the activities of the proteinases could reflect, as a whole, those of muscle fibres with rimmed vacuoles.

We confirmed the observation of Ii *et al.* (1986) that cathepsin B is involved in the formation of rimmed vacuoles. Differing from their observation, our data revealed that the biochemical activity and immunohistochemical reactivity of cathepsin H were lower and weaker than those of cathepsins B and L. However, biochemical analysis of cathepsin H in the present study was performed by using the substrate Arg-MCA, which could be digested by other aminopeptidases as well, so the contribution of other aminopeptidases to the level of cathepsin H activity should also be considered. Since cathepsin H cannot degrade any native myofibrillar proteins except troponin T and tropomyosin (Katunuma and Noda, 1982; Katunuma and Kominami, 1987), participation of this enzyme in muscle fibre degradation might not be as important as that of cathepsins B or L. Our results thus suggest that cathepsins B and L are more important than cathepsin H in rimmed vacuole formation.

In the present study, muscle from the patient with non-rimmed vacuole formation (Case 6) showed the highest degree of cathepsin B activity, as well as a significantly increased cathepsin B and L activity. This fact suggests that increased cathepsins B and L are not limited to rimmed vacuoles. However, the ratios of cathepsin B and L to acid phosphatase or β-D-glucosidase are significantly increased in patients with rimmed vacuoles but not in the disease controls. This would imply that the cathepsin L increase is disproportionately high in lysosomes represented by rimmed vacuoles as opposed to lysosomes represented by non-rimmed vacuoles.

We demonstrated the strongest immunoreactivity of liver cathepsin L in and around rimmed vacuoles. This observation was confirmed by evidence from biochemical and Western blot analyses, and is a new observation, since cathepsin L has not previously been identified at the sites of rimmed vacuoles in human diseased muscle. If antibody against muscle cathepsin L had been used, different results may have been obtained. However, molecular homology between liver and muscle cathepsins was evident, since immunoblotting of muscle and liver cathepsins B and L gave the same molecular mass immunoreactive bands. Moreover, Gal and Gottesman (1988) reported that human procathepsin L cDNA detected a human procathepsin L mRNA with the same molecular mass in various tissues tested. Thus there may be considerable homology between the sequences of the liver and muscle cathepsins, giving rise to antisera with similar characteristics.

The most potent endopeptidases are lysosomal cathepsins, in which cathepsin L has the strongest endopeptidase activity (Katunuma and Kominami, 1987). Cathepsin L is thought to participate mainly in autophagy (Ii *et al.*, 1985; Kominami *et al.*, 1987). Towatari *et al.* (1978) reported that cathepsin L extensively degrades native high molecular mass proteins. In contrast, cathepsin B is thought to participate mainly in heterophagy, since invading macrophages contain a much higher level of cathepsin B than cathepsins H or L (Katunuma and Kominami, 1987). Cathepsin L may thus be involved in the degeneration of muscle fibres with rimmed vacuole formations. The present study provides the first convincing evidence that cathepsin L is present in relation to the rimmed vacuoles in diseased human muscle and that the rimmed vacuoles are probably formed by the autodigestion of myofilaments.

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TRANSIENT GLOBAL AMNESIA

A CASE CONTROL STUDY

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SUMMARY

A case control study of transient global amnesia (TGA), transient ischaemic attacks (TIA) and normal controls is described. Each of the 51 TGA patients, selected between January 1985 and March 1990, was compared with four controls (two TIAs and two normals) for the presence of vascular risk factors (hypertension, diabetes, smoking habits, cholesterol, triglycerides and haematocrit levels, heart disease, previous stroke), previous TGA, migraine, psychiatric illness and recent head trauma. Patients with TGA had less diabetes, hypercholesterolaemia and hypertriglyceridaemia than TIA. TGA subjects had significantly more hypertension (odds ratio = 3.31) and migraine (odds ratio = 8.67) than normal controls. During a mean of 17.4 mths of follow-up (range 1–96 mths), three subjects had recurrent TGA, one sustained a TIA and a minor stroke, but none had seizures. Thrombo-embolism and epilepsy are unlikely to be the cause of this benign disorder. The role is stressed of appropriate precipitants, including haemodynamic changes, and of individual susceptibility (of which migraine is probably a marker) in the genesis of TGA.

INTRODUCTION

Transient global amnesia (TGA) is an episodic dysfunction of the central nervous system, during which there is a sudden loss of declarative memory for recent events without other neurological signs or symptoms, namely without any disturbance of vigilance, language, cognition, praxis or visuospatial functions (Bender, 1956; Fisher and Adams, 1958, 1964; Caplan, 1985). Its annual incidence has been estimated to be at minimum 3.4 per 100 000 (Miller *et al.*, 1987*a*; Hodges and Warlow, 1990; Koski and Marttila, 1990).

The aetiology of TGA remains unclear. It is also debatable whether TGA corresponds to a clinical entity with a unique pathophysiology or to a syndrome that has several causes. In the absence of a hypothetical biological marker of TGA, two methods can be used to address this issue. The first consists of performing dynamic ancillary examinations such as EEG (Fisher and Adams, 1964; Tharp, 1969; Cole *et al.*, 1987; Miller *et al.*, 1987*b*; Jacome, 1989), Doppler, measurements of cerebral blood flow (CBF) or of metabolic activity of the brain during an episode of TGA (Trillet *et al.*, 1987; Fayad *et al.*, 1990; Stillhard *et al.*, 1990) in order to confirm or exclude the several proposed aetiologies: vascular, epilepsy or migraine. However, TGA is not very common and most patients are not seen during the acute episode, or do not present when and where these facilities are available. Also, TGA episodes are short-lived, while some of these techniques are time consuming to set up and run. For these reasons, the number

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of patients examined during an episode by these techniques is small and provides conflicting results.

The second method consists of comparing TGA patients with matched populations afflicted by disorders such as stroke, migraine and epilepsy, which have been proposed as putative causes for TGA. However, few case control studies have been conducted and their results are also contradictory. Two of these studies (Kushner and Hauser, 1985; Guidotti *et al.*, 1989) suggest that TGA is a vascular event, either thrombo-embolic or vasospastic. Two other publications stress a link to migraine (Ghidoni *et al.*, 1988; Hodges and Warlow, 1990), while one suggests that TGA is occasionally related to epilepsy (Hodges and Warlow, 1990).

The present work is a case control study of TGA, transient ischaemic attacks (TIA) and normal controls.

METHODS

We performed a prospective case control study in a group of consecutive patients with TGA collected between January 1985 and March 1990. To be included, patients had to have had an episode of transient memory deficit according to the definition given in the Introduction (Caplan, 1985). These attacks had to have been witnessed by a capable observer and there should have been no accompanying focal neurological symptoms or signs. Headache, nausea/vomiting and drowsiness were allowable as associated symptoms during TGA. Patients who suffered a head injury within the 72 h preceding the amnestic period were not included.

Fifty-one cases which fulfilled these criteria were selected. The majority were referred by other neurologists who were aware of our study. Four referred patients were excluded: unwitnessed attack, one; psychogenic amnesia, according to the Diagnostic and Statistical Manual of Mental Disorders DSM III (American Psychiatric Association, 1980) definition, two; fall with head trauma immediately preceding the attack, one.

All patients were interviewed and examined by us during the attack (six cases) and/or some days after. In the first interview the patient and the witness were asked about characteristics of the attack, precipitating factors or activity preceding the attack, cerebrovascular risk factors (hypertension, smoking, hypercholesterolaemia, hypertriglyceridaemia, heart disease, diabetes, high haematocrit) and relevant previous medical history [previous TGA, migraine with or without aura (defined according to the Headache Classification Committee of the International Headache Society criteria, 1988), psychiatric illness, epilepsy and recent head trauma]. Hypertension and diabetes were defined according to the WHO criteria. Hypertension: systolic BP >160 mmHg and/or diastolic BP >95 mmHG on two occasions or subjects on antihypertensive treatment; diabetes: fasting glucose >140 mg/dl or random glucose >200 mg/dl. Hypercholesterolaemia was said to be present if fasting cholesterol >240 mg/dl; hypertriglyceridaemia present if fasting triglycerides >200 mg/dl, and the haematocrit high if >50%, according to the National Consensus Conference (Conferencia Nacional de Consenso, 1988). Smokers were defined as patients who were current smokers at the time of the attack. Patients with structural or ischaemic heart disease and arrhythmias were considered to be suffering from heart disease.

The following investigations were performed whenever possible: EEG, CT scan, carotid duplex scan, transcranial Doppler and neuropsychological evaluation using the Weschler Memory Scale. Patients were then asked to come to our clinic annually or sooner if TGA recurred or any new neurologic symptom developed. For those patients who failed the follow-up we conducted an interview by telephone.

Controls

For each index (TGA) patient, four controls of the same sex and age (±5 yrs) were selected: two TIAs (Group 1) and two controls from a general practitioner's list (Group 2).

Group 1. TIAs (79 carotid, 17 vertebrobasilar, six both carotid and vertebrobasilar) were selected from patients registered in our stroke database since 1985, where demographic and vascular risk factors were documented.

TGA/TIA comparisons were not performed for migraine, psychiatric disease or head trauma, due to lack of data.

Group 2. 'Normal' controls were selected from the list of a general practitioner working in a western suburb of Lisbon (Estoril). Demographic data, vascular risk factors, history of head trauma, migraine and psychiatric illness were collected prospectively, using the same definitions as for TGA patients, in consecutive subjects attended by this physician since 1987. Blood cholesterol, triglycerides, haematocrit and glucose were measured if recent values were not available. The reasons for consultation were: routine check-up in 30%; arthritis in 20%; gastrointestinal complaints in 7%; control of hypertension and other vascular risk factors in 16%; and other health problems in 27%. When more than two controls for each index were available, the first two to come were chosen.

Statistical methods

Comparison of the prevalence of risk factors and other prior medical features in TGA, TIA and normal controls was performed using χ^2 statistics, odds ratios and its 95% confidence intervals using the Mantel-Haenszel procedure (Breslow and Day, 1980).

RESULTS

Demographic data and risk factors

Fifty-one TGA cases were studied, 26 male and 25 female. Mean age was 59.8 yrs (SD = 10.5 yrs) ranging from 21 to 79 yrs. Females were significantly older than males ($t = 2.01$, $P < 0.05$).

The majority of TGA patients had none (12) or only one (17) vascular risk factor, 14 had two and eight had three or more. Hypertension was the predominant risk factor (28 cases, 55%) followed by hypercholesterolaemia (15 cases, 29%) and smoking (20%) (Table 1). Seven patients (14%) suffered from heart disease: angina, three; congestive

TABLE 1 RISK FACTORS IN TGA AND CONTROLS

Risk factor	*TGA*	*TIA*	*Normal controls*
Hypertension	28 (55%) (40–69)	58 (57%) (47–67)	26 (26%) (17–34)
Smokers	10 (20%) (10–33)	23 (23%) (14–31)	22 (22%) (14–30)
Cholesterol >240 mg/dl	15 (29%) (18–44)	49 (48%) (38–58)	41 (40%) (31–50)
Heart disease	7 (14%) (6–26)	22 (21%) (14–30)	24 (24%) (15–32)
Stroke	5 (10%) (3–21)	4 (4%) (1–10)	3 (3%) (0.6–8)
Haematocrit >50%	3 (6%) (1–16)	7 (7%) (3–14)	6 (6%) (2–12)
Triglycerides >200 mg/dl	2 (4%) (0.5–14)	42 (48%) (32–51)	11 (11%) (5–17)
Diabetes	0– (0–7)	19 (19%) (11–26)	8 (8%) (3–15)

Ninety-five percent confidence intervals in parentheses.

heart disease, one; mitral valve prolapse, one; calcified aortic valve, one; premature beats, one. Three had a high haematocrit. Five patients had a history of previous stroke: TIA, one; minor stroke, three; type unknown, one. Six patients had a previous TGA and 13 a history of migraine. Four patients reported psychiatric illness (depression) in the past.

TGA precipitating events and associated symptoms

In 35 cases the attack was closely related to a precipitating event. We grouped these precipitant events as shown in Table 2. Sexual activity was considered an emotional precipitating event, as in three patients the attack started some time (minutes) before sexual intercourse. In two patients the attack occurred during cerebral digital intra-arterial angiography and the images obtained did not show any abnormality suggesting posterior circulation vasospasm. Eleven patients complained of headache during and after the attack. Six of those had a history of migraine. Other associated symptoms were vomiting/nausea (11 patients), drowsiness (six) and dizziness (three).

TABLE 2 TRANSIENT GLOBAL AMNESIA PRECIPITATING EVENTS

Precipitating events	*No of cases*
Effort/sport	9 (6/3)
Sex/driving/emotion	11 (3/2/6)
Bathing/heat exposure	8 (3/5)
Valsalva manoeuvre	4
Angiography	2
Dental extraction	1

Ancillary procedures

Electroencephalography was performed in 44 patients. In three cases EEG was obtained during the attack. EEGs were normal in 30 patients, including all ictal recordings. Seven patients had temporal slowing (θ and δ waves) more evident on the left side; three showed temporal paroxysmal discharges (bursts of θ and sharp waves in two cases; θ and small spikes on hyperventilation in another); two had unspecific abnormalities (fast activity and asymmetry of amplitude between left and right temporal leads). Two patients had focal temporal slowing during EEG sleep recording.

Forty-one patients had CT scan (in the majority of cases with contrast). None had hippocampal or thalamic infarcts. Unrelated abnormalities were found: lacunes in three cases, an internal carotid aneurysm, a falx meningeoma and calcifications in three patients (basal ganglia, frontal and cysticercosis). Questionable areas of hypodensity (temporal and parietal) were found in two patients.

From the 27 carotid duplex scans carried out significant stenosis was found in only one case. The vertebrobasilar circulation was studied by transcranial Doppler in eight patients. This investigation did not show any abnormality.

Case control study results

Comparing the association of vascular risk factors in TGA patients and in the two control groups, we found that TIA patients had significantly more risk factors than the other two groups (TIA versus TGA, $\chi^2 = 19.01$, $P = 7.8^{-4}$) and that risk factors in TGA and normal controls had a similar distribution ($\chi^2 = 1.07$, d.f. = 4, $P = 0.90$). Each vascular risk factor was then compared in patients with TGA and TIA using the χ^2 test and the Mantel Haenszel estimate of the odds ratio. A lower proportion of patients with TGA had diabetes, elevated triglycerides and high cholesterol than did patients with TIA (Table 3).

The same procedure was used to compare vascular risk factors and previous medical history in patients with TGA and normal controls. The incidence of migraine and HTA was significantly higher in TGA patients than in the controls (Table 4).

TABLE 3 CASE CONTROL STUDY. TGA VERSUS TIA

Risk factor	χ^2	*MH odds ratio*	*95% confidence interval*
Diabetes	$P = 2.42^{-3}$	0	(0–0.214)
Triglycerides >200 mg/dl	$P = 4.03^{-6}$	0.222	(0.0547–0.675)
Cholesterol >240 mg/dl	$P = 0.0277$	0.483	(0.236–0.943)
Haematocrit >50%	NS	0.500	(0.0810–2.34)
Heart disease	NS	0.611	(0.261–1.37)
Stroke	NS	0.769	(0.302–1.90)
Smoking	NS	0.812	(0.360–1.86)
Hypertension	NS	0.909	(0.471–1.75)

TABLE 4 CASE CONTROL STUDY TGA VERSUS NORMAL CONTROLS

Risk factor	χ^2	*MH odds ratio*	*95% confidence interval*
Hypertension	$P = 3.323^{-4}$	3.31	(1.75–6.70)
Stroke	NS	3.33	(0.838–18.9)
Smoking	NS	0.889	(0.424–1.85)
Haematocrit >50%	NS	0.800	(0.159–3.72)
Heart disease	NS	0.524	(0.228–1.14)
Cholesterol >240 mg/dl	NS	0.452	(0.222–0.874)
Triglycerides >200 mg/dl	NS	0.364	(0.0844–1.23)
Diabetes	NS	0	0–0.586)
Previous medical history			
Migraine	$P = 5.907^{-5}$	8.67	(2.66–44.6)
Psychiatric illness	NS	1	(0.299–3.34)

Follow-up

Forty-eight patients were followed up from 1 to 96 mths (mean 17.4 mths; SD 19.8). One patient had both TIAs and a minor vertebrobasilar stroke during follow-up. This patient had a carotid stenosis and mitral valve prolapse. Three patients had a recurrent TGA at 4, 30 and 60 mths after the first one.

DISCUSSION

Collecting data on the epidemiology of TGA and comparing these patients with those afflicted by disorders with a putative similar aetiology is, as stated in the Introduction, a potentially useful approach to clarifying the nature of TGA.

Our sample largely confirms the demographic features, the good prognosis and the low risk of subsequent stroke in TGA found by others (Shuping *et al.*, 1980; Caplan, 1985; Kushner and Hauser, 1985; Hinge *et al.*, 1986; Miller *et al.*, 1987*a*; Rebucci and Stracciari, 1988; Guidotti *et al.*, 1989; Hodges and Warlow, 1990).

As far as we know only four case control studies have been performed to date. The Kushner and Hauser study (1985) was retrospective and compared 18 patients with 90 non-ischaemic neurological controls. Guidotti *et al.* (1989) studied prospectively 30 TGA patients, matched for age and sex with 30 TIA patients and 30 subjects with depressive neurosis. All cases were observed during the attack. Ghidoni *et al.* (1988) compared 77 TGA with two control subjects, sex and age matched, admitted for stroke or peripheral nerve disorders. Finally, the largest sample (114 TGA, 51 retrospective and 63 prospective) was studied by Hodges and Warlow (1990) comparing the cases with two control groups, 212 TIA patients and 109 normal community-based controls.

The results of these five studies (including ours) are somewhat contradictory with respect to three possible mechanisms for TGA: epilepsy, vascular disease and migraine (Olivarius and Jensen, 1979; Caplan *et al.*, 1981; Crowell *et al.*, 1984). The possibility of TGA being a manifestation of mesial temporal lobe epileptic discharges (Cantor, 1971; Greene and Bennett, 1974; Gilbert, 1978; Fisher, 1982) is not supported by our series, at least for the majority of patients. In fact, only three out of 44 patients had this type of discharge in EEG. None of our patients had a previous history of epilepsy or turned out to develop seizures during follow-up. Moreover, all EEGs performed during the attacks were normal and all patients in whom TGA recurred had a normal EEG. These results are in conflict with those reported by Hodges and Warlow (1990) but in accordance with Kushner and Hauser (1985), Guidotti *et al.* (1989) and with the majority of the authors who performed acute EEGs (Jaffe and Bender, 1966; Tharp, 1969; Cole *et al.*, 1987; Miller *et al.*, 1987*b*; Jacome, 1989). The discrepancy between Hodges and Warlow's series and the other case control studies may be due to its methodology. About one-half of Hodges and Warlow's cases were included retrospectively and in some cases patients or witnesses were interviewed some years after the initial attack. This time-lag makes their statements less reliable and could lead to some misdiagnosis of TGA in case of temporal lobe epilepsy. It has been suggested that TGA might be due to a vascular event with either a thrombo-embolic or a haemodynamic pathophysiology (Heathfield *et al.*, 1973; Mathew and Meyer, 1974; Rowan and Protass, 1979; Shuping *et al.*, 1980; Jensen and Olivarius, 1981; Cattaino *et al.*, 1984; Kushner and Hauser, 1985; Matias-Guiu *et al.*, 1986; Guidotti *et al.*, 1989; Frederiks, 1990; Torun *et al.*, 1990). Results from case control studies are also conflicting in relation to this issue. Kushner and Hauser (1985) concluded that TGA was definitely closely linked to cerebrovascular disease. However, their study had the smallest sample of all case control studies (18 cases). Moreover, 66% of their patients had sustained prior cerebral ischaemia, introducing a bias in subsequent results, namely the high recurrence of stroke and incidence of infarcts detected by CT among their TGA patients. In both our study and that of Ghidoni *et al.* (1988), hypertension was more common in TGA subjects than in normal controls, and TGA subjects had lower blood cholesterol and triglycerides than stroke patients. In contrast, Hodges and Warlow (1990) did not find a similarity between their TGA and TIA groups. There are, however, two problems with their TIA group. The proportion of amaurosis fugax in their TIA controls (31%) is higher than that found in community studies, i.e. one in 18 (6%) TIAs (Ueda *et al.*, 1987) and in other TIA samples, e.g. 12% reported by Bogousslavsky *et al.* (1986) and Hass *et al.* (1989), probably due to some referral bias. It is known that amaurosis fugax is a TIA subgroup strongly associated with extracranial vessel and generalized atherosclerotic disease and has a prognosis and prevalence of risk factors different from that in TIA not associated with amaurosis fugax (Harrison and Marshall, 1985; Hurwitz *et al.*, 1985; Amaurosis Fugax Study Group, 1990). On the other hand, their normal control group had a very high prevalence of HTA (according to WHO definition) (48.9%), higher than that found in our controls (25%) or in the Guidotti *et al.* (1989) study (17%). This high percentage of hypertension may be the result of the method used to select controls. In fact, controls were selected from among 200 appropriate subjects receiving a letter asking them to participate in the study. It is possible that people with known risk factors were more likely to answer this type of request. In any case, both our study and the English study demonstrated that the number and prevalence of risk factors are lower in TGA than in TIAs. Although in the Guidotti *et al.* (1989) study the prevalence of risk factors was similar in TGA and TIA, only TIA carried a risk of subsequent stroke.

In the majority of our cases the investigations performed to look for evidence of arterial disease or ischaemic infarcts, i.e. carotid duplex scan, transcranial Doppler and CT scan showed no abnormalities. Only one patient who had mitral valve prolapse and extracranial vessels disease sustained TIAs and a minor stroke during follow-up. All these data make a thrombo-embolic hypothesis for the pathogenesis of TGA seem unlikely. The prevalence of migraine in our TGA group was higher than that found in normal controls. The three patients in whom TGA recurred and half of the patients with a history of previous TGA had migraine. Several authors (Olivarius and Jensen, 1979; Caplan *et al.*, 1981; Crowell *et al.*, 1984) related TGA to migraine, suggesting that TGA is a migranous manifestation. However, unlike migraine, TGA occurs mainly in elderly patients and there is an age difference between sexes that is not present in migraine. Precipitating factors are also different, as most TGA precipitants can induce a rise of blood pressure or produce other haemodynamic modifications.

Despite these conflicting results from case control studies some general conclusions can be reached: TGA is a disorder of middle and old age and occurs in groups of individuals in whom there is a high incidence of migraine. The TGA population differs from the TIA population in the lower incidence of vascular risk factors, the benign prognosis and the absence of demonstrable extra or intracranial vessels abnormalities. Previous HTA and events inducing haemodynamic changes, e.g. a rise in blood pressure, seem to play a role in its precipitation. For an individual who suffers a TGA the risk of a recurrent episode is higher than in the normal population, thus indicating that there is an individual susceptibility to this phenomenon. Two hypotheses are suggested to explain this susceptibility. First, TGA-prone individuals may harbour a peculiar vascular anatomy, such as a unilateral hypoplasia of one or more small vessels supplying anatomical areas subserving declarative memory. Haemodynamic changes in the hypoplasic side could induce transient unilateral ischaemia leading to a memory deficit (Müller, 1990).

Alternatively a disturbance of neurotransmission similar to that proposed for migraine (Raskin, 1989) might also explain TGA. It is known that effort, emotion or stress, common precipitants of TGA, increase the activity of locus coerulus neurons. These noradrenaline producing cells are in close connection with the serotoninergic system (Malmgren, 1990). In a susceptible individual with unstable serotoninergic centres, that could in some instances lead to migraine attacks (Raskin, 1989), the above-mentioned precipitants could produce TGA by two possible mechanisms: a vasospastic response due to the combined actions of noradrenaline and serotonin on vulnerable areas such as the paramedian thalamus (Plum, 1989) or an inhibitory action on the hippocampal cortex (similar to the spreading of depression).

This mechanism is compatible with the fact that the caudal portion of the dorsal raphe and cells in the median raphe project to the hippocampus (Molliner, 1987). This interpretation is also in accord with recent suggestions that separate serotoninergic projections may serve different behavioural functions (Mulligan and Törk, 1988). An alternative explanation suggested by Olesen and Jørgensen (1986) is that strong emotional events might liberate glutamate, which is present in large amounts in the hippocampus eliciting spreading depression and amnesia.

Although establishing a link between emotional precipitants and TGA, this hypothesis does not explain the association between migraine and TGA, since glutamate is not thought to have a major role in the pathogenesis of migraine.

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COGNITIVE PERFORMANCE IN MULTIPLE SYSTEM ATROPHY

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SUMMARY

The cognitive performance of a group of patients with multiple system atrophy (MSA) of striato-nigral predominance was compared with that of age and IQ matched control subjects, using three tests sensitive to frontal lobe dysfunction and a battery sensitive to memory and learning deficits in Parkinson's disease and dementia of the Alzheimer type. The MSA group showed significant deficits in all three of the tests previously shown to be sensitive to frontal lobe dysfunction. Thus, a significant proportion of patients from the MSA group failed an attentional set-shifting test, specifically at the stage when an extra-dimensional shift was required. They were also impaired in a subject-ordered test of spatial working memory. The MSA group showed deficits mostly confined to measures of speed of thinking, rather than accuracy, on the Tower of London task. These deficits were seen in the absence of consistent impairments in language or visual perception. Moreover, the MSA group showed no significant deficits in tests of spatial and pattern recognition previously shown to be sensitive to patients early in the course of probable Alzheimer's disease and only a few patients exhibited impairment on the Warrington Recognition Memory Test. There were impairments on other tests of visual memory and learning relative to matched controls, but these could not easily be related to fundamental deficits of memory or learning. Thus, on a matching-to-sample task the patients were impaired at simultaneous but not delayed matching to sample, whereas difficulties in a pattern-location learning task were more evident at its initial, easier stages. The MSA group showed no consistent evidence of intellectual deterioration as assessed from their performance on subtests of the Wechsler Adult Intelligence Scale (WAIS) and the National Adult Reading Test (NART). Consideration of individual cases showed that there was some heterogeneity in the pattern of deficits in the MSA group, with one patient showing no impairment, even in the face of considerable physical disability.

The results show a distinctive pattern of cognitive deficits, unlike those previously seen using the same tests in patients with Parkinson's and Alzheimer's diseases, and suggesting a prominent frontal-lobe-like component. The implications for concepts of 'subcortical' dementia and 'fronto-striatal' cognitive dysfunction are considered.

INTRODUCTION

In contrast to the extensive investigation of cognitive deficits in Parkinson's disease (PD), Huntington's disease (HD) and progressive supranuclear palsy (PSP) (for a review *see* Brown and Marsden, 1988), there has not been a single neuropsychological study of multiple system atrophy (MSA), a condition which accounts for 5–10% of parkinsonians. Multiple system atrophy is a term used to describe a progressive neurological condition, usually incorporating a parkinsonian syndrome (striato-nigral degeneration)

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and often with additional autonomic failure (Shy-Drager syndrome) or cerebellar and/or pyramidal signs [olivopontocerebellar atrophy (OPCA)] (Berciano, 1982; Oppenheimer, 1983; Quinn, 1989). Multiple system atrophy appears to have distinct neuropathological signs, as shown from the recent findings of glial cytoplasmic inclusions, not only in those regions where cell loss and gliosis are classically found in MSA, such as the putamen, but also in the primary and premotor cerebral cortex and the paracentral gyrus (Papp *et al.*, 1989; Nakazato *et al.*, 1990). As in PD, the brains of patients with MSA show profound depletion of forebrain dopamine, noradrenaline and (more variably) acetylcholine (Spokes *et al.*, 1979).

Cognitive deterioration is not generally considered to be an integral feature of MSA (Quinn, 1989). Although coincidental Alzheimer's disease can occur (Trotter, 1973; Kosaka *et al.*, 1981), this is seen at a rate no higher than in the general age-matched population. The clinical impression is that global cognitive impairment is not a consistent feature of patients with MSA. However, in our experience routine neuropsychological assessment often reveals evidence of underfunctioning of variable and as yet undefined cognitive deficits.

In this study we investigated cognitive function in a group of patients with MSA of the striato-nigral type, concentrating on tests that we have found to be sensitive to frontal lobe damage and PD. In recent papers (Downes *et al.*, 1989; Owen *et al.*, 1991) we introduced an attentional set-shifting paradigm based on learning theory and showed that unmedicated PD patients performed at least as poorly as either medicated patients, who were later in the course of PD, or patients with neurosurgical lesions of the prefrontal cortex. However, patients with temporal lobe excisions or amygdalohippocampectomy are not impaired in this test, showing that the frontal lobe deficits have considerable neural specificity. Another test suitable for assessing frontal lobe function is the Tower of London planning task, which Shallice (1982) showed was sensitive to anterior cortical damage. Owen *et al.* (1990*a*) confirmed that performance on a similar computerized version of the test is impaired, in terms of both accuracy and speed measures of thinking, in patients with neurosurgical lesions of the frontal (but not temporal) cortex. The computerized version allowed the inclusion of a motor control condition, where the subject had to make moves defined by the computer program, thus enabling true thinking time on the test problems to be calculated by subtraction. Whereas frontal patients were found to be less accurate on this task, and slower to think about the problems subsequent to the first move (Owen *et al.*, 1990*a*), patients medicated for PD were no less accurate, but were significantly slower in making their initial move (Morris *et al.*, 1988; Owen *et al.*, 1990*b*, unpublished data). Finally, we employed a test of spatial working memory that has again been found to be sensitive to frontal lobe damage, partly because of the use of inefficient strategies for reducing the load on working memory (Owen *et al.*, 1990*a*). Performance on a similar test had previously been found to be normal in PD patients on medication (Morris *et al.*, 1988). Thus, in summary, we employed one test (attentional set-shifting) identifying similar deficits in PD and frontal lobe patients, another (Tower of London) which produced qualitatively different deficits, and a third (spatial working memory) sensitive to frontal lobe damage but not to unmedicated or mild cases of medicated PD.

In order to define the specificity of any deficits found with the tests of frontal lobe function, we also administered, to most of the patients, tests from a battery which we had previously shown to be sensitive to memory and learning deficits in PD and Alzheimer's disease (Sahakian *et al.*, 1988).

SUBJECTS

Multiple system atrophy (MSA) patients

A consecutive series of 16 patients diagnosed as clinically probable MSA of striato-nigral type (MSA-SND) was studied. All patients were diagnosed at the National Hospital for Neurology and Neurosurgery, Queen Square, London, according to the criteria set out by Quinn (1989) (*see* Table 1). Cases 1 – 15 had a poor or absent response to levodopa treatment. Case 16 had greater than 50% response with dyskinesia and fluctuations, but within 2 yrs had developed respiratory stridor, frequent falls, postural faintness and urinary disturbance with abnormal sphincter EMG. The duration of the disease averaged 6 yrs, taken from the time of initial symptoms. All but two patients had received a CT scan. One of these two received instead an MRI scan. Six of the patients also underwent [^{18}F]fluoro-dopa PET scans. Only two of the 16 MSA patients were not receiving medication at the time of testing. All of the remainder were receiving levodopa preparations or bromocriptine. Two patients were receiving the anti-cholinergic drug benzhexol (Artane).

TABLE 1. CLINICAL FEATURES PRESENT IN MSA GROUP

Case	*Sex*	*Parkinson*	*Cerebellar*	*Pyramidal*	*Autonomic*	*Duration of disease (yrs)*	*Hoehn and Yahr stage*
1	M	+	−	+	+	9.5	III
2	M	+	−	+	+	4.5	IV
3	M	+	+	+	+	7.5	V
4	M	+	+	+	+	2	III
5	M	+	+	+	+	7	III
6	M	+	+	+	+	7	III
7	F	+	−	+	+	6	III
8	M	+	+	+	+	9	V
9	M	+	+	+	+	6	IV
10	M	+	+	−	+	10	IV
11	M	+	−	−	+	6	III
12	M	+	−	+/−	+	5.5	IV
13	M	+	−	+/−	+	2.5	V
14	M	+	−	−	+	10	III
15	M	+	+	−	+	2	III
16	F	+	−	−	+	4	IV

+ = present, +/− = brisk reflexes+equivocal plantar responses; − = absent.

Normal controls

Control subjects were drawn from a large population of volunteers aged between 35 and 70 yrs from London, Cambridgeshire and Newcastle upon Tyne (North-East Age Research Panel) These controls had no history of neurological or psychiatric disorder. From this population, two control groups were selected separately for the Working Memory and Planning (control group 1; $n = 16$) and for the Visual Memory batteries (control group 2; $n = 15$), matched for age and NART IQ. The performance of the MSA group on the ID/ED attentional shift task was evaluated by comparison with a control group ($n = 32$, two for each MSA patient) chosen on a blind basis, but matched overall for age, NART IQ and male:female proportion.

Informed consent was obtained from all patients and controls.

METHODS

Clinical neuropsychological assessment

All patients and controls were tested on the National Adult Reading Test (NART) (Nelson, 1982) to obtain an estimate of their optimal intellectual ability. All but one of the patients received routine clinical assessment in the Department of Psychology, The National Hospital, including a shortened form of the WAIS or WAIS-R (Wechsler, 1955, 1981). Verbal IQs were prorated from the Vocabulary, Similarities, Arithmetic and Digit Span subtests. Performance IQs were prorated from the Picture Completion, Block Design and Picture Arrangement subtests. Similarly, all but one MSA patient received the Recognition Memory Test (Warrington, 1984). Thirteen patients received tests of visual perception (Unconventional Views and Incomplete Letters tests) (Warrington and James, 1967; Warrington and Taylor, 1973). For the McKenna Naming Test (McKenna and Warrington, 1983) scores were available for nine of the 16 patients. Time constraints and physical disability made it impossible for all tests to be administered in the clinical session.

Experimental computerized tests

The main testing procedures were taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB), a series of cognitive tests run on an Acorn BBC Master128 Microcomputer, with a high resolution Microvitec 30 cm VDU and a Microvitec Touchtec 501 touch-sensitive screen. These were generally administered in two test sessions, one of approximately 90 min and one of 45 min. Subjects were seated approximately 0.5 m from the monitor and it was explained that they would have to respond to stimuli by touching the screen.

They were introduced to the apparatus by way of a 'sensorimotor screening task' in which they were asked to respond to a series of flashing crosses on the screen by placing the index finger of their preferred hand on the centre point of each cross. All subjects satisfactorily completed this task and so were allowed to proceed to the following experimental tests. The first three tests were then taken from the CANTAB Working Memory and Planning tests (*see* Owen *et al.*, 1990*a*).

Spatial short-term span. In this computerized version of the Corsi Block Tapping task, the ability of subjects to remember a sequence of squares highlighted on the screen was determined. Each trial began with the same arrangement of nine white 3 cm squares arranged quasi-randomly in the space of the screen. Subjects were instructed to observe the boxes, as some would change colour one after the other. Their task was to remember the location and the sequential order of the boxes changing colour. During each series, one box would change colour for 3 s and then return to white before the next in the sequence changed to the same colour. The subject was then prompted by a tone to repeat the sequence by touching the boxes in the same order. During this response sequence, each selected box changed to the same colour for 1 s and a feedback tone sounded. Following one demonstration trial by the experimenter, the task began at the simplest level of difficulty with a two box sequence. After each successful trial, the number of boxes changing in the next sequence was increased by one to a maximum of nine boxes. After an incorrect attempt at any particular level, an alternative sequence of the same length was presented. This continued until the subject had failed three consecutive trials at any one level. During each trial, a number in the bottom left-hand corner of the screen indicated the length of the current sequence. Also, all boxes changed to the same colour within each series, although on any two adjacent sequences different colours were used to minimize interference. The spatial short-term memory span was calculated as the highest level at which the subject had successfully recalled at least one sequence of boxes. The number of errors made in attaining this level was also recorded.

Spatial working memory task. In this task the subject was required to 'search through' a number of coloured 3 cm boxes presented on the screen, by touching each one in order to 'open it', thus revealing its contents (*see* Fig. 1A). The colours of the boxes stayed constant within a trial, but varied over trials. The goal was to collect blue 'tokens' hidden inside the boxes, and once found, to use them to fill an empty column at the side of the screen. The subjects were instructed that at any one time there would be a single token hidden inside one of the boxes. Their task was to search until they found it, at which point the next token would be hidden. The key instruction was that, once a blue token had been found within a particular box, then that box would not be used again to hide a token for that particular trial. Since every box was used once, on each trial the total number of blue tokens to be found corresponded to the number of boxes on

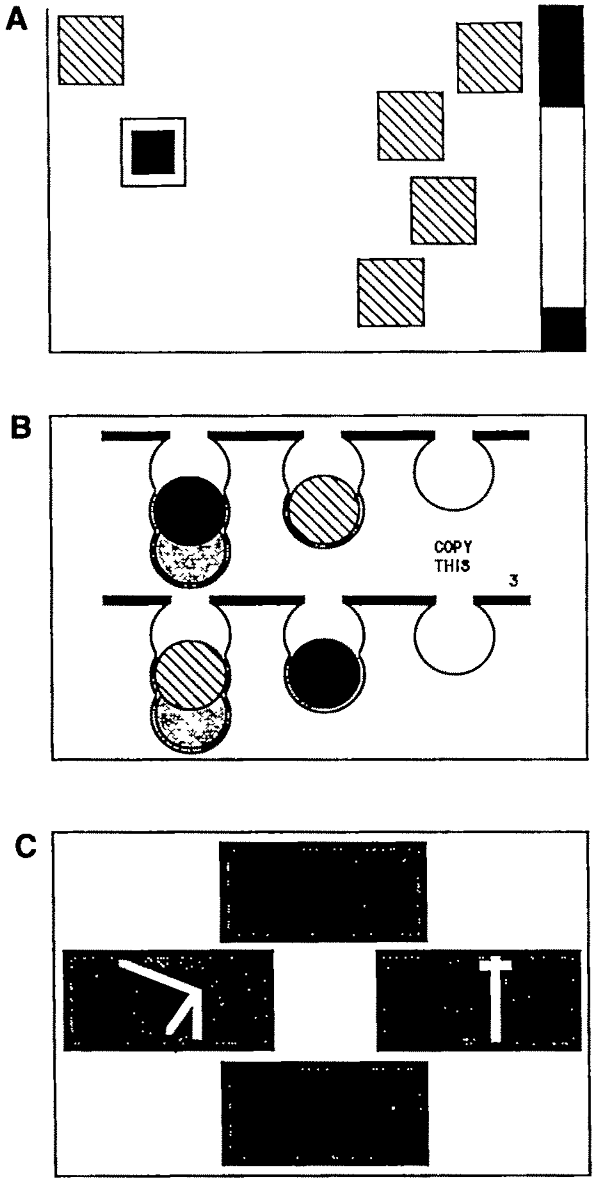


FIG. 1. A, the arrangement of boxes on the sceen for the spatial working memory task. The example shows a six box trial, in which one of the boxes has just been chosen to reveal a 'blue token' which can now be added to one already in the column on the right-hand side of the screen. This leaves the subject with four more tokens to find, in boxes in which they have not previously been located. B, a sample three move problem for the modified Tower of London task. The goal position of the balls is shown in the top arrangement. C, sample pairs of compound stimuli and their arrangement on the screen in the ID/ED attentional set-shifting task.

the screen. In this task, two types of search error are possible. First, a subject may return to open a box in which a blue counter has already been found (a 'between search' error). Secondly, a subject may return to a box already opened in the same search sequence (a 'within search' error). Subjects could search the boxes in any order, but for control purposes, the number of boxes visited (excluding errors), before a token was found was determined by the computer. Thus, each subject received the same degree of feedback prior to the first error. After two practice trials with three boxes, there were four test trials with each of four, six and finally, eight boxes. The task was scored according to the number of between and within search errors at each level of difficulty. An efficient strategy for completing this task is to follow a predetermined search sequence, beginning with a particular box and then returning to start a new sequence with that same box as soon as a token has been found. The extent to which this strategy was used was calculated from the number of search sequences starting from the same box, within each of the six and eight box problems. The total of these scores provided a single measure of strategy for each subject, with a high score representing low use of the strategy and a low score representing more extensive usage.

Planning task. This task is closely related to one developed by Shallice and McCarthy, the 'Tower of London', that provides simpler versions of the 'Tower of Hanoi' problem (Shallice, 1982). Two sets of three coloured balls were presented, one in the top half of the screen and one in the bottom half. These were described to the subject as snooker balls since they appeared to be hanging in 'pockets' or 'socks' (*see* Fig. 1B). There were three pockets in each half of the screen, one that could clearly hold three balls, one that could hold two balls, and one that could be completely filled by one ball. On each trial a red ball, a blue ball and a green ball were placed in predetermined positions in the pockets of each of the two displays. The subject was asked to rearrange the balls in the bottom display, such that their positions matched the 'goal' arrangement in the top half of the screen. A ball could be moved by the subject first touching it and then touching an empty position in one of the other pockets. Once selected, a tone sounded and the rim of the ball began to flash, indicating that it was ready to be moved. At any time, the subject could cancel a selected ball by touching it a second time. 'Illegal' moves, such as trying to remove a ball while there was another sitting above it in the same pocket, were carefully explained to the subject and, if attempted, they were registered, but evoked no response from the computer.

The starting position of the balls was varied such that in any particular trial the solution could only be reached after a minimum of two, three, four or five moves. Subjects were instructed to examine the position of the balls at the beginning of each problem and attempt to solve it in the minimum possible number of moves. This was given to them verbally and displayed on the screen throughout each trial. They were encouraged not to make the first move until they were confident that they could execute the entire sequence needed to solve the problem. The maximum moves allowed corresponded to twice the minimum number possible plus one, or plus two, in the case of five-move problems. Following the successful completion of each problem, the VDU displayed the word 'FINISHED', before moving on to the next trial. The program stored the number of moves required by the subject to rearrange the balls and measured the selection and movement latencies for both the first and the subsequent moves. After six practice problems with one and two moves, the subject was given two each of two and three move problems and four each of four and five-move problems. These test problems corresponded exactly to those used in the original Tower of London test.

For each test problem, a 'yoked control'. condition was employed to provide baseline measures of motor initiation and execution times. On each trial of this control condition, the subject was required to follow a sequence of single moves executed by the computer in the top half of the screen by moving the corresponding ball in the lower arrangement. Thus, initially the two arrangements differed by just one ball. Once the subject had made the appropriate move, the top arrangement changed again, so that the subject had to make another single move. The test was 'yoked' to the main test in the sense that in each trial, the movement of the balls was an exact replication of those moved by the subject in the corresponding test trial. The measurement of selection and execution latencies in this control condition provided baseline estimates of motor initiation and execution times.

Test trials and 'yoked' control trials were arranged in four blocks of six problems each. The first six test trials were given (two problems at each of two, three and four moves), followed by their corresponding 'yoked' control trials. Then the remaining six test problems were presented (two at four moves and four at five moves), followed by their yoked control trials. Between each block change there were two practice trials to ensure that the requirements of the current set of tasks had been fully understood

(i) *Accuracy measures of performance* Across the 12 test problems, two measures relating to the number of moves required to reach solution were calculated: (1) the *mean number of moves above the minimum possible* (*'excess moves'*) provided a general measure of group performance at each level of difficulty;

(2) the *proportion of problems solved in the minimum number of moves* (*'minimum move solutions'*) provided more specific information about task difficulty.

(ii) *Latency measures of performance.* Baseline measures of motor initiation and motor execution times were extracted from the 12 'yoked control' trials. In all cases, latencies were recorded in centiseconds and converted to seconds for the purpose of presentation. The *'motor initiation time'* was the mean time between the onset of each problem, and the initiation of the first move (i.e. a correct touch of the required ball). The *'motor execution time'* was the time between touching the first ball and completing the sequence of single moves that comprise the whole problem. Since these control problems were yoked to the test problems, the total execution time was divided by the number of moves to provide an estimate of the average movement time per move.

The motor initiation and execution times were used to derive estimates of planning or 'thinking' time in the main task. Two separate estimates were calculated. In each problem, the *'initial thinking time'* was the time between the presentation of the problem and the first touch, minus the corresponding motor initiation time, as calculated from the 'yoked control' task. The *'subsequent thinking time'* was the time between the selection of the first ball and the completion of the problem minus the total motor execution time from the corresponding control problem. Since this measure clearly varied with problem length, subsequent thinking time scores were divided by the number of moves to give an estimate of the average thinking time 'per move'. In this way, pure estimates of initial and subsequent thinking times were derived, unconfounded by motor initiation or execution times.

Intra- and extra-dimensional (ID/ED) set-shifting paradigm. The test set-up and stimuli were shown to the subjects. Four rectangular boxes, to the top and bottom and to the right and left of centre, appeared on the screen. Two of these contained the test stimuli but the boxes used changed from trial to trial. Subjects were instructed in the following way:

'Now you can see two patterns. One of the patterns is correct. You must point to the one you think is correct. There is a rule you can follow to make sure you make the correct choice each time. The computer will be keeping track of how well you are doing and when it is clear that you know the rule the computer will change it, but this will not happen very often. To begin with, there is nothing on the screen to tell you which of the two patterns is correct, so your first choice will be a simple guess. However, the computer will give a message after each attempt to tell you whether you are right or wrong. You can start now.'

The test then proceeded through a number of stages, each with a different contingency, up to a maximum of nine (*see* Fig. 1c). For each, continuation to the next stage was dependent on a criterion of six successive correct discriminations being reached. If criterion was not reached at the 50th trial of a stage, then the test was discontinued and subjects did not proceed to the following stage. The order of discrimination was fixed, so that the ED shift always followed the ID shift. However, previous work has established that comparable effects are found when the alternative ordering is used (Roberts *et al.*, 1988). More detailed rationales for the exact design of the test can be found in previously published articles (Roberts *et al.*, 1988; Downes *et al.*, 1989).

To begin with, subjects were given a simple simultaneous discrimination in which the stimuli varied along only one of the two 'dimensions' for deriving the stimuli. These dimensions were purple-filled shapes or white lines. The starting dimension was balanced across subjects and groups. A response to one of the two boxes containing the stimuli resulted in an auditory tone, together with visual feedback which informed the subjects of the correctness of their responses. This feedback was in the form of the words 'correct' and 'wrong' presented respectively in green and red lettering above the middle two boxes. The same feedback was used for each of the subsequent stages. After 1.5 s the screen cleared and an inter-trial interval of 1 s was begun.

Following the initial simple discrimination (SD), the remaining eight stages were as follows. For the second stage, simple discrimination reversal (SDR), the discriminanda remained the same, but the previously incorrect choice became the correct one and vice versa, i.e. the contingencies were reversed. At the third stage, compound discrimination (with spatially separated elements) (C-D), the second dimension was introduced with one exemplar of each dimension paired together to form a compound stimulus in two of the response boxes. To succeed, a subject had to continue to respond to the correct exemplar of the previous stage. For this and all subsequent stages, exemplars of the different dimensions were paired in a pseudorandom fashion so that all four possible compound stimuli were used, with the constraint that runs of no more than three trials with the same pairings were allowed. The stimuli for the fourth stage, compound discrimination (with elements superimposed) (CD) and subsequent stages were also compounds, but the two exemplars from the different dimensions were superimposed, with the white line always in the foreground. The contingencies were again unchanged from those for the previous two stages. A reversal then occurred at the fifth stage (CDR). New exemplars for both dimensions were introduced at the sixth stage, the intra-dimensional shift (IDS), but the relevant dimension (i.e. shapes or line) was unchanged from Stage 1. This was followed by a further reversal at the seventh stage (IDR). For the penultimate stage, the extra-dimensional shift (EDS), new exemplars were again introduced, but success at this point was dependent on the subject shifting response set to the exemplars of the previously irrelevant dimension. Finally, contingencies were reversed to the previously incorrect exemplar of the new dimension (EDR). The main measure of performance on this task was the stage successfully attained.

Tests of visual memory and learning. It was not possible to administer the complete battery to all of the MSA patients because of the occasional need to limit the length of the test session in order to avoid fatigue. The patients received computerized tests of visual memory and learning identical to those previously described in detail (Sahakian *et al.*, 1988). These included tests of pattern and spatial recognition (n = 15) simultaneous and delayed matching to sample (n = 13) and a conditional visuospatial associative learning task (n = 11). In the pattern recognition test, subjects were shown a number of abstract visual patterns, one after another on the VDU, before being asked to point to which one of two they had previously seen. There were two blocks of 12 patterns to remember. In the spatial recognition test, a white square moved around the VDU screen to five locations in turn. In the test phase, the subjects were asked to point to the locations where they had previously seen the square, in a two-alternative forced choice procedure. The test comprised four blocks of five locations each. In the matching to sample test, subjects were shown a sample abstract visual stimulus on the VDU and were then asked to point to the one which matched exactly this sample from an array of four such stimuli. In the delayed matching-to-sample component, the sample stimulus was turned off before the matching stimuli appeared, either 0 s, 4 s, 8 s or 16 s later. There were five trials in each condition. In the conditional visuospatial associative learning task, subjects were required to remember or learn the locations of abstract visual stimuli in not more than 10 repeated trials. The test began with the requirement to remember the location of only one stimulus, then there were sets of two, three, six and eight stimuli to remember. If the subject failed to reach criterion at any stage, the test was discontinued.

Statistical analysis

For most of the dependent variables, analysis of variance was used. Where appropriate the data were transformed to meet the assumptions of this method. For most of the test variables, the ANOVA model was a two factor design which included a Between Subjects factor (Group) and a Within Subject factor (e.g. Difficulty Level). Analysis of significant interactions was made by determining the Simple Main Effects (Winer, 1971, pp. 544–545) and with appropriate *post hoc* comparisons based on the Newman-Keuls test.

For the ID/ED task, the data for the numbers of subjects passing or failing each stage of the test were cast into contingency tables and analysed using the Likelihood Ratio method (Kullback, 1968; Robbins, 1977). The Likelihood Ratio method is particularly useful for analysing data with small cell frequencies and the resulting 'information' statistic (2i) is distributed as χ^2 (Kullback, 1968).

The complete control samples were also used to obtain a percentile range of performance on each test for the purpose of assessing the significance of deficits in individual patients.

RESULTS

Clinical neuropsychological tests

The MSA patients and controls were matched for age and NART IQ. The mean age and NART estimated IQ for the MSA group was 55.2 (SD = 7.7) yrs and 111.5 (SD = 8.7), respectively. The mean ages of the three control groups were: Group 1, 54.6 yrs (SD = 7.3); Group 2, 56.5 yrs (SD = 5.8); Group 3, 56.6 yrs (SD = 5.7).

The respective mean NART estimated IQs for the control groups were 112.6 (SD = 6.7), 111.7 (SD = 7.5) and 111.9 (SD = 7.0). Table 2 shows the characteristics of the individual patients for age, NART IQ, WAIS Verbal and Performance IQs, and Recognition Memory test scores. Only three of the MSA group had a discrepancy between their NART IQ and WAIS Verbal IQ scores of more than 10 points. Thus, the majority of the group showed no evidence of intellectual deterioration. Similarly, in spite of the fact that these patients were motorically impaired, only three had WAIS Verbal Performance discrepancy scores greater than 10 points. No clear pattern of deficits was revealed in the subtest scores. For the Recognition Memory test, on the verbal version one patient was severely impaired and another three showed mild deficits when compared with their expected scores. On the visual version two patients were severely impaired and a further three were mildly deficient. Thus, nine out of 15 patients performed entirely satisfactorily on this test, showing no memory deficits. No patient out of the 13 assessed showed any perceptual deficit. No naming difficulties were evident in the nine patients who were tested on the McKenna Naming test.

TABLE 2 NEUROPSYCHOLOGICAL CHARACTERISTICS OF MSA GROUP

					Recognition Memory Tests (scaled score)	
Case	*Age*	*NART IQ*	*WAIS Verbal IQ*	*WAIS Performance IQ*	*Words*	*Faces*
1	61	114	124*	108*	15	12
2	53	106	99*	90*	7	7
3	54	121	114	116	12	13
4	54	104	112*	112*	7	9
5	54	113	113	105	13	13
6	44	124	126	135	15	17
7	54	93	93	97	7	7
8	54	121	127	114	10	8
9	64	107	107	104	15	13
10	66	117	103	107	12	3
11	51	116	102*	90*	10	9
12	59	114	101	nt	10	nt
13	57	121	122	116	15	16
	69	102	nt	nt	nt	nt
15	50	110	105	120	3	4
16	39	101	98*	99*	13	15

nt = not tested. * Predicted WAIS IQs converted from WAIS-R (Crawford *et al* , 1990).

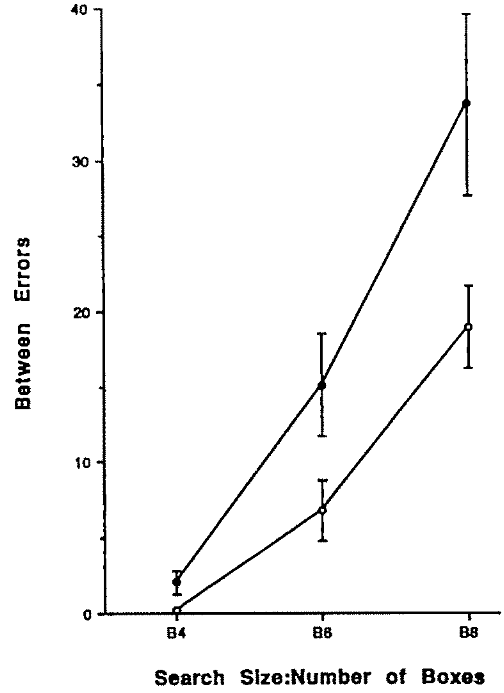
Experimental computerized tests

Spatial span

There were no significant differences in spatial span between the matched controls and the MSA group (F = 2.89, d.f. = 1, 30; $P > 0.05$). The mean spans attained for each group were: Matched Controls, 5.7 (SD = 1.14); MSA, 5.1 (SD = 0.93). In attaining their highest span score the MSA group averaged only one error and the control group, 0.4 (F = 3.64, d.f. = 1, 30; $P > 0.05$).

Tests sensitive to frontal lobe dysfunction

Spatial working memory. Figure 2 shows the mean and SEM number of between search errors at each level of difficulty (four, six and eight boxes) for the control and MSA groups. Analysis of variance showed significant main effects of Group (F = 5.91, d.f. = 1, 30, $P = 0.02$) and Difficulty Level (i.e. number of boxes, four, six or eight) (F = 54.11, d.f. = 2, 60; $P < 0.001$). There was also a significant interaction between Group and Difficulty (F = 3.48, d.f. = 2, 60; $P < 0.05$). *Post hoc* analyses of variance at each Difficulty Level showed that the MSA group was significantly worse at the level of eight boxes (F = 11.1, d.f. = 1, 30; $P < 0.01$) and the difference at the level of six boxes approached significance (F = 3.52, d.f. = 1, 30, ns). Within search errors were variable and at a low level, and so were summed over the levels of difficulty. The control group averaged 3.38 (SD = 3.79) and the MSA group 10.0 (SD = 15.82) errors, a non-significant difference (F < 1.0).



FIG, 2 Between search errors on the spatial working memory test at different levels of task difficulty for the MSA (●) and matched control (○) group

For the strategy score there was no significant difference between the groups [F < 1.0, d.f. = 1, 30; $P > 0.05$; mean (SD) scores, controls 34.4 (4.08) and MSA 35.56 (5.88)].

Tower of London. There was a non-significant trend for the MSA patients to be significantly less accurate on the minimum moves measure of accuracy of thinking (F = 3.63, d.f. = 1, 30; $P > 0.05$). Mean (SD) values were as follows: controls, 9.3 (1.58); MSA 8.3 (2.2). For the excess moves measure, mean (SD) scores are shown in Table 3. Analysis of variance showed no group effect (F = 1.92, d.f. = 1, 30; $P > 0.05$). The mean scores for the latency measures are also shown in Table 3. For initial thinking time, there was no significant group difference at any level of difficulty (i.e. two, three, four or five moves) (F = 1.63, d.f. = 1, 30; $P > 0.05$). There was a significant effect of difficulty (F = 21.67, d.f. = 3, 90; $P < 0.001$), largely because of the large increase after the easier two move problems. However, there was no significant interaction between Group and Difficulty (F < 1.0, d.f. = 3, 90; $P > 0.05$).

TABLE 3 SUMMARY OF MEAN (SD) SCORES ON TOWER OF LONDON PLANNING TEST

	Control group (n = 16)	*MSA (n = 16)*
Excess moves above the minimum		
Two moves	0	0.03 (0.13)
Three moves	0.25 (0.53)	0.50 (0.81)
Four moves	0.89 (0.74)	1.44 (0.97)
Five moves	1.33 (1.41)	1.59 (1.52)
Initial thinking time(s)		
Two moves	1.49 (0.80)	1.80 (1.51)
Three moves	6.82 (4.25)	10.69 (8.87)
Four moves	9.33 (5.16)	10.54 (8.03)
Five moves	11.57 (6.60)	12.81 (7.57)
Subsequent thinking time(s)		
Two moves	0.47 (0.56)	0.69 (0.83)
Three moves	0.58 (0.88)	2.58 (3.49)
Four moves	2.09 (2.78)	4.06 (2.58)
Five moves	1.49 (1.86)	2.45 (1.98)

For subsequent thinking time, there were significant main effects of Group (F = 8.28, d.f. = 1, 30; $P < 0.01$) and Difficulty (F = 8.96, d.f. = 3, 90; $P < 0.001$), with longer thinking times for MSA patients at the three, four and five move problems (*see* Fig. 3).

As expected, movement times in the yoked control task differed significantly among groups. The MSA group were significantly slower than the controls; for initial movement time, F = 4.95, d.f. = 1, 30; $P < 0.05$: for subsequent movement time, F = 17.89, d.f. = 1, 30; $P < 0.001$. The mean values for initial movement time across task difficulty varied from 2.98 to 4.42 s for the MSA group and 2.08 to 2.38 s for the control group. Parallel data for subsequent movement time were: MSA, 3.55–4.40 s; control, 1.82–2.28 s.

ID/ED set-shifting paradigm. Figure 4 shows the proportion of subjects passing each stage of the ID/ED shift paradigm. These data were analysed using the Likelihood Ratio method for contingency tables. Approximately 88% of control subjects passed all stages of the test, whereas only 56% of the MSA group did so. This difference was significant overall (2i = 5.63, d.f. = 1, $P < 0.02$). Further analysis focused on individual stages of the test, taking into account only subjects attempting those stages. This showed that a significant point of failure occurred at the EDS stage in the MSA group. Here, two

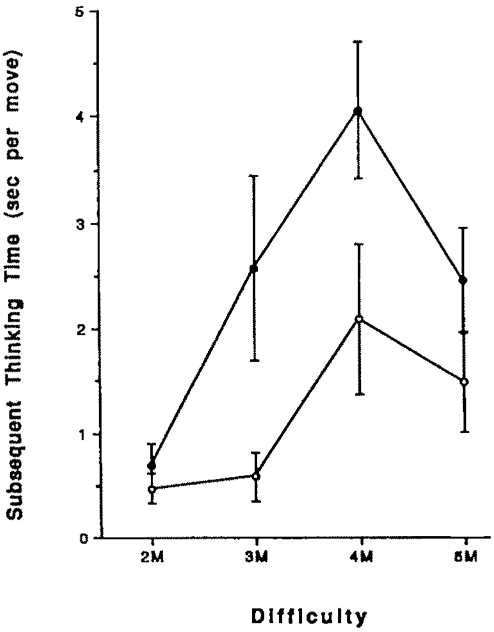


FIG. 3. Subsequent thinking time at two, three, four and five move problems on the Tower of London task. ●, MSA; ○, controls

out of 32 (6.66%) of control subjects failed, compared with six out of 15 (40%) of the MSA patients (2i = 7.12; d.f. = 1, $P < 0.01$). Thus, the MSA patients exhibited a significant and selective deficit in switching attention between the two dimensions.

Tests of visual memory and learning

The main results are summarized in Table 4.

Pattern and spatial recognition memory. Neither of these tests showed any significant differences between the MSA and control groups.

Simultaneous matching to sample. There was a significant impairment in the MSA group in the simultaneous matching component but not in delayed matching to sample performance, even as a function of delay ($F < 1.0$, d.f. = 3, 78; $P > 0.05$).

Conditional visuospatial associative learning. All of the controls successfully learned within 10 trials each set of pattern-location associations, up to and including the final set of eight patterns. In the MSA group, two patients failed to reach criterion at the level of six patterns. For the purposes of analysis of trials and errors to criterion over the entire test, these subjects received scores of 10 (i.e. the maximum score) trials and an error score one more than that of the worst control subject actually attempting the most difficult level. Despite these adjustments, there were no significant differences between the two groups over the test as a whole (*see* Table 4). Inspection of the data at separate levels of difficulty within the test sequence showed that there were apparent group differences before the most difficult sets of six and eight stimuli. For example, at the easiest levels of the task where the locations of only one, two or three stimuli have to be remembered, only four out of 15 of the control subjects made any errors

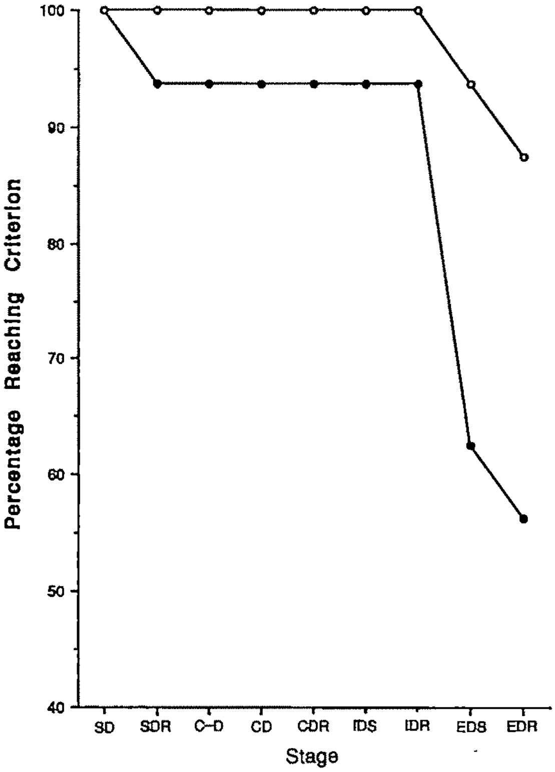


FIG. 4 Cumulative proportion of MSA patients (●) (n = 16) and controls (○) (n = 32) reaching criterion at various stages of the ID/ED attentional set-shifting paradigm. *See* text for definitions of each stage

TABLE 4 SUMMARY OF RESULTS FOR VISUAL MEMORY AND LEARNING BATTERY

	MSA group	*Control group*	*F ratio (d.f.) P<*
Pattern recognition (maximum 24)	19.3 (4.1)	20.3 (2.1)	F < 1.0 (1, 28) ns
Spatial recognition (maximum 20)	14.8 (2.8)	15.8 (1.9)	F = 1.3 (1, 28) ns
Simultaneous MTS (maximum 5)	4.4 (1.1)	5.0 (0.0)	F = 4.5 (1, 26) *P* < 0.05
Delayed MTS (maximum 5)			
0 s	4.54 (0.88)	4.87 (0.35)	
4 s	4.62 (0.51)	4.60 (0.83)	
8 s	3.92 (1.44)	4.00 (0.93)	
16 s	3.77 (1.42)	4.40 (0.83)	
Overall (maximum 20)	16.84 (6.4)	17.88 (3.28)	F = 1.3 (1, 26) ns
Conditional learning			
Total trials to criterion	17.1 (7.0)	14.3 (3.4)	F = 1.9 (1, 24) ns
Total errors to criterion	28.6 (26.0)	21.3 (13.7)	F < 1.0 (1, 24) ns

Values shown are mean (SD) values. ns = not significant (median 0, range 0−3), whereas nine out of 11 MSA patients committed errors (median 3, range 2−20). As the distribution of these data violated the assumptions of analysis of variance, the cumulative error scores were compared with a Mann-Whitney U test, which confirmed a significant difference between the groups ($U = 23.5$, $P < 0.01$).

REPRESENTATIVE CASES

The following four cases (*see* Table 1) illustrate the range of cognitive performance found in the MSA group. Of these Case 3 was the only one to show no cognitive deficits on any test, Case 9 was the most representative of the group as a whole and Cases 7 and 12 showed atypical patterns of a broader range of impairment.

Case 3

This administrator developed poor balance, slurred speech and urinary frequency in June 1982. Neurological examination a year later revealed an akinetic-rigid syndrome with a slight tremor of the left arm, Parkinson's disease was diagnosed and Madophar was prescribed with benefit. In November 1983 he developed urinary retention. Prostatectomy was largely unsuccessful, and by a year later he had developed nystagmus and heel-shin ataxia. He was referred to us in January 1989, when, at the age of 59 yrs, a diagnosis of MSA was made, and he was tested on levodopa medication. His physical condition confined him to a wheel-chair. His CT scan showed generalized atrophy that was, however, greatest in the cerebellum. On neuropsychological testing he had a NART IQ equivalent of 121, a WAIS Verbal IQ of 114 and WAIS Performance IQ of 116. His visual perceptual skills were normal.

His performance on computerized tests showed a normal spatial span (5). On the spatial working memory task he made only 23 between-search errors, a score at the 75th percentile for his age and a superior strategy score, in the top 5% for his age group. On the Tower of London task, his performance was well within the normal range for all measures. He successfully completed the attentional set-shifting task.

He was also most competent on tests of memory. For example, his Warrington Recognition Memory Test scores were in the bright average range. He scored 92% correct on the pattern recognition and 90% on the spatial recognition tests of the computerized tests. His performance on the delayed matching to sample test was error free. He successively completed the conditional visuospatial associative learning task with no errors, even at the most difficult level of eight items. This latter performance is exceptional, even for normal healthy subjects of high IQ.

Overall, it is clear that this man exhibited a high degree of intellectual competence, in spite of gross physical disability. He died in July 1990, 18 mths after testing. Post-mortem examination confirmed the clinical diagnosis of MSA.

Case 9

This shop-owner originally developed nocturia in 1982. One year later, a large prostate was operated on by the supra-pubic route, with good result. However, he then developed slurred speech and began to drag his left foot. He was first seen by a neurologist in December 1986, when a parkinsonian syndrome with left-sided pyramidal signs was found. By February 1988, when he was tested, he had developed additional cerebellar signs and clinically probable MSA was diagnosed. He had a normal CT scan. On neuropsychological testing in February 1988 at age 64 yrs, he had a NART IQ equivalent of 107, a WAIS Verbal IQ of 107 and a Performance IQ of 104. His visuospatial tasks were weak, but within the normal range for his age. His score on the McKenna Naming Test was in the superior range. There was thus little evidence of any generalized intellectual deterioration. When tested he was under levodopa medication. His spatial span was normal (5). He performed at a very low level on the spatial working memory test, making 53 errors at the six box stage and 98 errors at the eight box stage. His strategy score, however, was in the normal range. On the Tower of London test he was only mildly slow in initially thinking about the two move problems, but was otherwise in the normal range. He failed the extra-dimensional shift in the attentional set-shifting paradigm.

His performance on tests of recognition memory was normal. For example, he attained excellent scores of 50/50 (verbal) and 46/50 (visual) on the Warrington Recognition Memory Test and 75% and 79% on computerized tests of spatial and pattern recognition memory. He was mildly impaired in reaching criterion in paired associates learning, although this deficit was not sustained at the most difficult level (8). Thus at the second test, at level 3 he made five errors, taking three trials, at level 6 he took six trials to reach criterion and made 18 errors, but on the immediately following level (8) he took only three trials in making five errors, a normal level of attainment. Finally, his scores on the matching-to-sample test were as follows. On the simultaneous version of the task and at 0 s delay he scored consistently 80%, whereas his performance with delays was error free. His performance on this test thus resembled those shown previously by patients with Parkinson's disease (Sahakian *et al.*, 1988). Overall, his performance on the computerized tests is consistent with frontal lobe dysfunction. This deficit is supported by clinical evidence of poor verbal fluency, difficulties with the Similarities subtest of the WAIS and concrete interpretations of proverbs

Case 7

This printer's assistant presented in 1982 with falls and postural faintness. A year later, she developed slowness and stiffness and Parkinson's disease was diagnosed. By 1988, additional pyramidal signs were present and a diagnosis of clinically probable MSA was made. Her CT scan revealed brain stem and cerebellar atrophy. She was receiving levodopa and imipramine at the time of testing when her age was 54 yrs. Her NART IQ equivalent was 93, her WAIS Verbal IQ 93 and her Performance IQ 97. Her naming skills were consistent with her low average intellectual ability. Her visual perceptual skills were normal. Overall, there was no evidence of generalized intellectual impairment. When tested in March 1988 her spatial span of 5 was in the average range. She scored normally on the test of spatial working memory. On the Tower of London test she was poor on both accuracy and latency measures, particularly at the three move stage and she failed at the extra-dimensional shifting stage of the attentional set-shifting paradigm. Therefore, although this woman was unimpaired on tests of spatial memory storage and spatial working memory, she exhibited deficits in both planning and attentional set-shifting.

On additional testing, she also showed a pattern of mild impairment on tests of visual recognition memory and learning. For example, on the Warrington Recognition Memory tests she scored 41/50 (verbal version) and 40/50 (visual version), these dull average scores being slightly below her predicted optimum level of performance. On computerized tests of spatial and pattern recognition she scored 45% and 60%, respectively, both scores being significantly below the fifth percentile for control performance. Although she scored 100% in a test of simultaneous matching to sample, she was impaired on delayed matching to sample at delays of 8 s (60%) and 16 s (60%). She successfully completed a test of visuospatial paired associated learning at the level of 8, but cumulatively made significantly more errors (34) and took significantly more trials (20) to reach criterion than controls.

In summary, this patient showed deficits in tests sensitive to frontal lobe dysfunction, but was also mildly impaired on tests of recognition memory and learning. The patient died in June 1989; no post mortem was carried out.

Case 12

This marine engineer had first presented with parkinsonism, diagnosed as Parkinson's disease, in December 1982. However, his response to levodopa therapy was minimal and his disability progressed. He developed several syncopal episodes, his speech became markedly hypophonic, and he developed a disproportional antecollis, but there were no pyramidal or cerebellar signs. A diagnosis of clinically probable MSA was made in June 1986. He was not under medication when tested at age 59 yrs in April 1988. He had a normal CT scan. On neuropsychological testing, his NART IQ equivalent was 114, giving an estimate of his premorbid intellectual ability within the bright average range. However, his WAIS Verbal IQ was only 101, suggesting mild to moderate intellectual deterioration. The Performance subtests of the WAIS were not administered in view of his physical disability. His visuospatial performance was weak, but within normal limits. Language functions were well preserved.

On the computerized testing, his spatial span was below average (4). For the spatial working memory task his total of 65 between-search errors was below the 10th percentile for his age. He showed no obvious search strategy, his score (47) being worse than any control subject. On the Tower of London he managed only four out of 12 problems in the minimum number of moves. Initial thinking time was significantly lengthened in two, three and four move problems and subsequent thinking time in three move problems. He did manage to complete the attentional set-shifting task.

His performance on memory tests was also somewhat inconsistent. Although performing at an average level on the Recognition Memory test for words and scoring 88% on the computerized pattern recognition test, he was deficient on the spatial form of the test (55%) and exhibited a delay-dependent deficit on the test of delayed matching to sample. He failed the conditional visuospatial associative learning task at the level of six items. In summary, despite his normal CT scan, this man showed mild to moderate generalized intellectual deterioration and specific deficits in certain tests of frontal lobe function and visual memory.

DISCUSSION

In this study we have provided evidence of cognitive dysfunction in patients with MSA, using three tests sensitive to the effects of frontal lobe damage. However, there was no consistent evidence either of deficits in tests of memory and learning or of generalized intellectual deterioration that has been observed in patients with probable dementia of the Alzheimer type (DAT), using the same tests. While some of the deficits seen in the MSA group resembled those we have defined in PD, there were also some differences from the profile of deficits seen in that condition.

Considering the nature of the deficits shown by the MSA group in more detail, there were many similarities to those seen previously after neurosurgical damage to the frontal lobe (Owen *et al.*, 1990*a*, 1991). For example, the MSA group showed patterns of deficits on the ID/ED set-shifting paradigm, quantitatively and qualitatively similar to those seen in frontal patients. On the spatial working memory test, the MSA group made significantly more between search errors, to a similar degree as following frontal lobe damage, although they did not show the same impairment in strategy seen in that group (Owen *et al.*, 1990*a*). Their performance on the Tower of London test was also qualitatively similar to that seen in frontal patients. For example, the MSA patients took significantly longer to think about the problems subsequent, but not prior, to the first move of the problems. This lengthened latency was not merely an artefact of the patients' motor impairment, as this was carefully controlled by subtracting the latency to make the same moves used to solve the problems when no planning was required. The MSA group was not significantly impaired on the other main measures of performance on the Tower of London test, although they showed a near significant tendency to show the same lack of accuracy of thinking as displayed by frontal patients. Overall, the pattern of performance of MSA patients on the accuracy and latency measures of the Tower of London test resembles that produced in the milder cases of planning dysfunction following frontal lobe damage. This pattern is markedly different from the one we have defined in PD, where there is strong evidence for lengthening of initial, but not subsequent thinking times on the Tower of London test (Morris *et al.*, 1988), a finding which we have recently replicated with exactly the same version of the test as used here on subgroups of PD patients with relatively severe, as well as moderate, disability (Owen *et al.*, 1990*b*, unpublished data). Therefore, based on these comparisons, it would appear that, whereas the cognitive deficits seen in PD, MSA and frontal lobe damage do have some gross similarities, the MSA profile is, if anything, more comparable with that seen in the frontal lobe patients than those with PD.

Although the MSA group exhibited deficits in each of the tests of frontal lobe function they did not necessarily show impairment in other cognitive domains such as perception or language. In addition, the deficient performance of the MSA group on the spatial working memory and planning tests could not be attributed to general problems in short-term memory for spatial information or in terms of the sequencing of responses, because the index of visuospatial span was normal in these patients. This preserved function stands in contrast to the reduced spatial span in patients with DAT reported by Sullivan *et al.* (1986) and also to patients with severe PD studied by us with exactly the same test (Owen *et al.*, 1990*b*, unpublished data).

In addition, there were no significant differences whatsoever in performance on the computerized tests of spatial and pattern recognition, which are also sensitive to deficits in patients with DAT and medicated PD (Sahakian *et al.*, 1988). This is in agreement with the overall performance on the Warrington Recognition Memory Tests, where only two patients had specific memory deficits and two showed mild impairment (*see* Table 2). The MSA group were inferior to the matched controls on the other two main tests of the visual memory battery, but in specific and unusual ways. Thus, on the matching-to-sample test they were significantly impaired at the simultaneous stage, where there is no mnemonic component, but showed normal delayed matching performance. This is the exact opposite of the pattern shown by patients early in the course of DAT (Sahakian *et al.*, 1988). The particular pattern of deficit in MSA is also distinct from that reported for PD (Sahakian *et al.*, 1988). Moreover, on the test of visual learning, unlike both patients with DAT and with PD (Sahakian *et al.*, 1988), the MSA patients performed surprisingly well at the more difficult levels of the task, but were inefficient at the earlier stages. Taken together with the deficient performance on the simultaneous component of the matching to sample test, but unimpaired performance on the delay component which immediately follows, this pattern of results is suggestive not of primary learning and memory deficits, but of problems in orientation or attention. These mask the patients' true potential for memory and learning, but can be overcome as the task becomes familiar and attentional resources are gradually marshalled. It is possible that the initial problems are consistent with impairments in attentional functions that depend on executive functions of the frontal lobes (Shallice, 1988).

Although the MSA patients showed a distinctive and significant profile of deficits as a group, there was some heterogeneity of cognitive dysfunction, with one case (Case 3) showing no discernible deficits, even in the face of severe physical disability, but others exhibiting clear impairments on a variety of different tests. The range of cognitive performance present in the MSA group is illustrated by the four case studies. Case 9 showed the most representative profile, with deficient performance on the three main tests sensitive to frontal lobe dysfunction, spatial working memory, attentional set-shifting and the Tower of London planning task, but no evidence of deficits of memory or learning and no signs of generalized intellectual impairment. By contrast, the less typical Cases 7 and 12 showed broader patterns of impairment which included deficits in memory and learning. Indeed, unlike all of the other MSA patients, the deficits in memory and learning for Case 12 resembled those found with the same tests in early cases of DAT (Sahakian *et al.*, 1988). This patient was one of only three who showed a significant NART-Verbal IQ discrepancy (*see* Table 2), indicating a degree of intellectual deterioration. Therefore, it appears that, in agreement with the clinical impression (Trotter, 1973; Kosaka *et al.*, 1981; Quinn, 1989), there is no compelling evidence of a progressive dementing disorder in MSA.

None of the major deficits in the MSA group were correlated significantly with disease duration or Hoehn and Yahr ratings of severity. The highest correlation found was between Hoehn and Yahr rating and subsequent thinking time at two moves on the Tower of London test ($r = 0.45$, $P > 0.05$). This once more underlines the relative independence of the cognitive from the motor deficits in MSA. Because some of the MSA patients were receiving a variety of drugs at different doses it is more difficult to look for precise associations between medication and cognitive impairment, but none were evident. Although formal ratings of depression were not obtained, it is most unlikely that the pattern of cognitive deficit described here can be explained simply in terms of underlying depression. First, in a recent study of elderly depressed patients (Abas *et al.*, 1990) there were large deficits in the same tests of visual memory and learning that were not apparent in the present MSA group. Secondly, it is difficult to account for the precise pattern of deficits in the MSA group in terms of depression, or indeed fatigue. For example, these patients often performed relatively better at the more difficult stages of the tasks, which is opposite to the pattern generally observed in depression (*see* review by Robbins *et al.*, 1992).

Ultimately, the profile of cognitive deficit in MSA must be explained in terms of the neural systems that are damaged in this condition. Despite the impairments in tests sensitive to frontal lobe dysfunction and the deficits in memory and learning in some patients seen here, the literature has reported no clear evidence of atrophy or observable changes in the cerebral cortex or hippocampus. In the forebrain, the main signs are striatal DA loss and degeneration of the striatum itself (Spokes *et al.*, 1979; Oppenheimer, 1983). Some studies employing neuro-imaging have demonstrated a relatively lower caudate uptake of [^{18}F]fluoro-dopa in MSA patients, in contrast to the relatively preserved uptake in this region in PD (Nahmias *et al.*, 1985; Rutledge *et al.*, 1987; Brooks *et al.*, 1990*a,b*).

Therefore, one obvious possibility is that the cognitive deficits seen in MSA are caused by striatal pathology, disturbing the neural circuitry intimately linking the frontal cortex to the striatum (Alexander *et al.*, 1986; Taylor *et al.*, 1986). An alternative, though not mutually exclusive, hypothesis is that the deficits do indeed depend upon the dysfunction of other forebrain structures that results from neurochemical pathology. For example, Spokes *et al.* (1979) report from four cases, clear evidence of disturbances in glutamatergic neurons in the hippocampus, and in the only region of neocortex assayed, the motor cortex. In addition, the cognitive deficit in MSA might also reflect deafferentation of the neocortex and other forebrain structures of chemically defined pathways originating in the 'isodendritic core' (Agid *et al.*, 1987). For example, there is evidence of noradrenergic depletion in the locus coeruleus and a number of forebrain regions, consistent with degeneration of the coeruleal cortical noradrenergic pathway (Spokes *et al.*, 1979). Moreover, as in both PD and DAT (Agid *et al.*, 1987) there is evidence of cholinergic deficits in the hippocampus, although in the four cases of MSA reported by Spokes *et al.* (1979) the reduction in hippocampal choline acetyltransferase activity varied from about 45% to 95%. Such observations have interesting implications for some of the individual data reported here, where, for example, visual memory and learning were also variably affected (Cases 7 and 12).

The pattern of deficits shown in MSA as impaired set-shifting on the ID/ED paradigm, deficient spatial working memory and slowness in thinking (or bradyphrenia) is perhaps comparable with the cluster of deficits sometimes called 'subcortical' as distinct from 'cortical' dementia (Albert *et al.*, 1974). The former syndrome has been suggested to subsume the cognitive and behavioural deficits shown by patients with pathology of the basal ganglia and other subcortical structures, including PD, HD and PSP, whereas the latter is more usually associated with DAT. On the basis of the present results, there is certainly some evidence to support a dichotomy between the cognitive profile in early DAT on the one hand and MSA, PD and HD on the other. For example, whereas patients with each of the latter disorders are impaired on the ID/ED attentional set-shifting task (Downes *et al.*, 1989, and unpublished results), no such deficit is associated with mild cases of DAT despite much more severe deficits in visual learning and memory (Sahakian *et al.*, 1990). However, the concept of subcortical dementia has been criticized on the grounds of the similarity of the cognitive profile to that produced by frontal lobe damage, resulting in the suggestion of a more appropriate term 'fronto-subcortical dementia' (*see* Cummings, 1986; Brown and Marsden, 1988). The comparison we have made between frontal lobe patients and the MSA group is clearly directly relevant to this issue. It does appear that the MSA syndrome is comparable with the effects of frontal lobe damage in many aspects, supporting the possibility of a 'fronto-subcortical' or perhaps more specifically, 'fronto-striatal' syndrome. However, a further comparison of interest is with the cognitive profile in PD, which appears distinct from that of MSA, both in terms of the breadth of cognitive deficits seen in the later stages of PD, and in terms of the qualitative nature of the deficits we have described above for the tests sensitive to frontal lobe dysfunction. These differences clearly warrant more detailed exploration, but their existence suggests that the syndrome of 'subcortical' or 'fronto-subcortical' dementia may well not be unitary in nature.

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THE INCIDENCE OF THE GRASP REFLEX FOLLOWING HEMISPHERIC LESION AND ITS RELATION TO FRONTAL DAMAGE

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SUMMARY

The grasp reflex and related prehensile phenomena were investigated in two studies. In Study 1, 491 patients consecutively admitted to the neurological wards of our department were tested with a standardized procedure. Grasping was found in 8% of brain-damaged patients and occurred predominantly in patients with single (14 cases) or multiple (10 cases) hemispheric lesions, accompanied by stable neurological symptoms. The locus of the lesion was either in the frontal lobe or in the deep nuclei and subcortical white matter. Grasping never occurred when the disease was confined to the retrorolandic regions.

Study 2 was designed to identify the frontal structures responsible for grasping. Forty-four patients who either showed grasping or had CT scan documentation of frontal damage were investigated. Grasping was found in 70% of patients who had involvement of the medial areas and was always associated with damage to the cingulate gyrus; the supplementary motor cortex was less consistently encroached upon. It also occurred following damage to the lateral motor and premotor areas, but only in 26% of cases. A few patients with grasping had deep lesions.

The clinical analysis of the symptom showed that it usually affected both hands, even when the lesion was unilateral, and that in most patients it did not manifest itself as a forced phenomenon, but could be modified by will, although it showed up again as soon as the patient's attention was diverted. Groping was more rarely found and the so-called grasp reaction was unusual. No hemispheric asymmetry in the occurrence of this set of phenomena was apparent.

INTRODUCTION

It has long been known that some brain-damaged patients show, in response to the tactile stimulation of their hands or even to the mere presentation of an object, a gamut of prehensile phenomena characterized by the tendency to catch hold of the object without any apparent intention to use it purposefully. Their manifestations are manifold and have been the subject of repeated descriptions and attempts at classification, which, following Seyffarth and Denny-Brown (1948), can be grouped under two main headings.

(1) *The grasp reflex* which is a stereotyped and relatively simple response, consisting of the progressive, forced closure of the patient's hand on the examiner's fingers, when they are slowly moved, exerting a strong pressure across the palm in an upward direction. Attempts to withdraw the fingers through the thumb-index cleft result in an increase of the strength of the grasp. Reported under different names: 'reflexe de la prehension' by Janischewski (1914), 'Zwangsgreifen' by Schuster (1923), 'tonic innervation' by Walshe and Robertson (1933), the grasp reflex has been the subject of fastidious analyses

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aimed at bringing out the circumstances favouring its appearance. Some authors (Schuster, 1923; Adie and Critchley, 1927) maintained that the effective stimulation to produce it was tactile, e.g. distally moving contact over the palm, while others (Walshe and Robertson, 1933) thought that grasping movements in response to objects seen or making contact with the skin of the hand have a volitional character and must be kept separate from tonic grasping elicited by flexor muscle stretching, which is reflex in nature. At the end of a careful analysis, Seyffarth and Denny-Brown (1948) came to the conclusion that the tactile pressure on the skin of the palm played a major role in triggering the contraction of the flexor and adductor muscles (the catching phase), while the stretching of the tendons simply acted to reinforce the contraction (holding phase). Findings consistent with this interpretation were provided not only by studies on monkeys (Rushworth and Denny-Brown, 1959), in which the grasp reflex produced by frontal lobe ablation disappeared after local anaesthesia of the palm with procaine, or ulnar and median nerve section at the wrist, but also by neurophysiological studies carried out in man (Shahani *et al.*, 1970; Cambier *et al.*, 1972).

Foot grasping has been described by Schuster and Pinéas (1926) and Goldstein (1938) as flexion and adduction of toes with curving of the sole, in response to a pressure upon the sole without moving the stimulus.

(2) *Instinctive grasp reaction.* The term covers a range of behaviours which share with the grasp reflex, the tendency to take hold of the object stimulus, but are differentiated by the type of stimulation suitable to elicit them, the greater variability of responses and the influence exerted by psychological factors. For descriptive purposes, five subvarieties (or subsequent stages) of this behaviour were distinguished by Seyffarth and Denny-Brown (1948).

Closing reaction. This occurs in response to a light stationary touch of any part of the hand, including the back. A sequence of finger movements begins that has the aim of adjusting the finger position so as to bring the stimulus to the centre of the palm.

Final grip. This occurs after a variable delay, occupied by the preliminary adjusting phase; fingers and thumb close around the stimulus.

Trap reaction. If the stimulus is removed in any direction, a sudden tightening of fingers occurs.

Magnet reaction. If the patient fails to hold the object as it is removed, the hand moves to follow it.

Instinctive groping. By a progressive retreat of the stimulus, as the hand approaches it, a pursuing phase is elicited.

Not all patients showing the grasp reflex also exhibited the instinctive grasp reaction and vice versa; from Seyffarth and Denny-Brown's paper (1948) it would appear that the former manifestation was thought to be more frequent than the latter. The 'instinctive groping' stage had already been described by Schuster (1923) and Adie and Critchley (1927) and can be evoked by visual stimuli, without previous tactile stimulation, especially when they are located in the same hemispace as the responding hand and are close to it (Magnani *et al.*, 1987).

In this context, it is worth mentioning another peculiar prehensile behaviour, which has recently been described (Lhermitte, 1983; Lhermitte *et al.*, 1986) almost always in association with the grasp reflex; namely, the utilization behaviour, characterized by the patient's tendency to grasp and use objects present in the environment. In the procedure followed by Lhermitte (1983), the behaviour was elicited first by putting an object in the patient's hand to stimulate grasping, then by abruptly withdrawing it to stimulate groping, and finally by simply presenting it. Shallice *et al.* (1989), however, have clearly shown that compulsive manipulation of objects can also occur when they are simply made available on the two ends of the testing desk, without any attempt to draw attention on them. It is interesting to remark that this behaviour can be limited to the hand contralateral to lesion. Walshe and Hunt (1936) were the first to document the symptom in the context of a study on grasping. While engaged in conversation, their patient tried every 20 s or 30 s to grasp with the right hand a cigarette that had been laid down upon the bed, though realizing that this was inappropriate and at times intervening with the left hand to block the right hand. A compulsive manipulation of familiar (but not unfamiliar) tools confined to the right hand was reported by Mori and Yamadori (1982) and by Motomura (1990) in patients with an infarct involving the left medial frontal lobe and the anterior corpus callosum. The behaviour was not inhibited by verbal command and was associated with the grasp reflex.

The grasp reflex is generally considered an index of frontal lobe pathology. This notion has gained wide acceptance and is mentioned by most authoritative textbooks, but a scrutiny of the literature reveals that the evidence supporting it is not so compelling as one would like, being mainly based on selected case reports and having to face the challenge represented by a few cases in which the lesion was non-frontal.

In the most comprehensive study on the subject, Seyffarth and Denny-Brown (1948), reported investigations on 68 patients having the grasp reflex but details were given for only 10 of them and, since the focus of the paper was on the conditions in which the reflex could be elicited and on its pathophysiological mechanisms, no attempt was made to relate the phenomenon to the locus of lesion. All other papers were concerned with single patients or a small number of patients who were reported just because they showed grasping. Although most of them suffered from frontal damage, there were also cases with lesion of the basal ganglia (Schuster, 1923; Janischewsky, 1928; Goldstein, 1931; Stief, 1932; Gullotta, 1933; Castaigne *et al.*, 1970), the parietal lobe (Feodorovoa, 1929, Case 5, cited by Bucy, 1931; Walshe and Hunt, 1936, Case 2), the temporal lobe (Goldstein, 1938, Case 4; Hécaen *et al.*, 1957, Case 8), the parieto-occipital region (Bucy, 1931) and there are even sparse reports of patients with a completely unexpected location of lesion, such as the occipital lobe (Mayer and Reisch, 1928), the fourth ventricle (Bucy, 1931), the cerebello-pontine angle (Foerster, 1933; Sittig, 1933) and the cerebellar hemisphere (Sittig, 1933). Grasping has also been found in dementia, degenerative as well as vascular (Paulson and Gottlieb, 1968; Cambier *et al.*, 1972; Tweedy *et al.*, 1982; Huff *et al.*, 1987; Bakchine *et al.*, 1989), in pseudobulbar palsy (Janischewsky, 1928) and in advanced Parkinson's disease (Huber and Paulson, 1986). Seyffarth and Denny-Brown (1948) went so far as to claim that grasping may even occur in many adult subjects without apparent brain injury, when their attention is distracted.

Groping also has been related to frontal pathology. However, in the four cases with pathological documentation reported by Castaigne *et al.* (1970) only one had frontal damage (bilateral anterior cerebral artery infarcts); the others had bilateral basal ganglia infarcts, Pick's disease and progressive supranuclear palsy.

What is badly needed to clarify the issue is a systematic investigation of the incidence of grasping in a large and unselected sample of patients with and without brain damage, and an attempt to relate its presence to lesions of definite cerebral areas, an approach that is now possible owing to the introduction of imaging procedures.

Here we present such a study and attempt to answer the following questions. (1) Is grasping an unequivocal sign of hemispheric pathology, or may it also appear in patients without brain disease or with brain disease not involving the hemispheres, or with hemispheric dysfunction without a macroscopic lesion? (2) In patients with hemispheric pathology, is grasping linked with damage to the frontal lobe in general and to some of its areas in particular, and how consistent is this association?

The research was carried out in two stages, the former aimed at assessing the frequency and specificity of grasping, the latter at enlarging the case material with damage to discrete frontal regions.

STUDY 1

The aim of this study was: (1) to develop a standardized procedure for uncovering the presence of grasping and related phenomena and to index their severity, and (2) to assess its association with damage to defined areas of the brain.

Patients

In an 8-mth period we attempted to test every patient admitted to the wards within the first few days of hospitalization. We tested 491 patients, representing 40% of total admissions. The only patients intentionally excluded were those who were comatose. Others were excluded unintentionally, due to shortness of hospitalization, readmission, oversight and absence of definite diagnosis. Tested patients were categorized as follows (*see* Table 1 for the number of patients in each group): (1) patients with clinical and, when available, CT scan signs of a single hemispheric lesion, still present at the time of testing (the great majority of these patients had vascular disease or tumours); (2) patients with sudden onset of focal hemispheric symptoms or signs, which had disappeared at the time of testing. These patients had a diagnosis of transient ischaemic attack (TIA) or reversible ischaemic attack (RIND); (3) patients with clinical, and when available, CT scan signs of multiple hemispheric lesions (vascular infarctions, metastases and multiple sclerosis); (4) patients with diffuse cortical disease. All but one of these patients had a diagnosis of Alzheimer-type disease; (5) patients with extrapyramidal signs, most of whom were diagnosed with Parkinson's disease; (6) patients with subtentorial pathology; (7) patients with subarachnoid haemorrhage and without focal

TABLE 1 STUDY 1 INCIDENCE OF G+ PATIENTS IN THE DIAGNOSTIC CATEGORIES EXAMINED IN STUDY 1

Group	*Case*	*G+ patients*	*%*
1. One hemispheric lesion (neurological signs +)	130	14	11
2 One hemispheric lesion (neurological signs −)	55	–	–
3. Multiple hemispheric lesions	53*	10	19
4. Diffuse disease	14	–	–
5. Parkinsonism and other extrapyramidal diseases	17	1	6
6. Subtentorial lesions	29	–	–
7. Subarachnoid haemorrhage	4	1	25
8. Epilepsy	38	–	–
9. No cerebral lesion	151	–	–
Total	491	26	5

* = 37 with vascular infarction, 11 with multiple sclerosis and five with metastases.

signs; (8) epileptic patients without evidence of accompanying cerebral pathology; (9) patients with disease not involving the brain.

Testing

A common feature of all of the testing procedures to be described below was that, while performing the manoeuvres to elicit the grasping phenomena, the examiner diverted the patients' attention from their limbs by asking questions about their disease or history and keeping the stimulated hand out of sight. If aphasia prevented verbal interaction, the patients' attention was diverted by asking them to look at different directions or to imitate buccofacial movements.

Grasp reflex

The examination was conducted with the patient lying on a bed. The examiner put his forefinger and middle finger on the thenar side of the palm at the level of the wrist and, exerting some pressure on the skin, moved them distally and withdrew them at the level of the metacarpophalangeal joints of the patient's thumb and index finger. The palm stimulation was repeated three times at short intervals, scoring the patient's reaction 0 if no finger flexion occurred, 1 if the patient's fingertips came into contact with the examiner's fingers without pressing against them and 2 if grasping progressively increased as the examiner tried to withdraw his fingers Patients who over the first three trials did not react to the stimulation, or had a total score of 3 or less, were considered negative. There were 25 patients with score 1−3 and note was taken of the group to which they belonged (*see below*). Patients with a score 4−6 (in fact, all had a score of 6) were considered positive and underwent the following testing procedures: (1) After a short interval, the manoeuvre was repeated a fourth time and if it resulted again in grasping (score 8), the examiner said 'Why are you grasping? I have not asked you to do it', and took note of the patient's comments; (2) for about 10 s the patient's attention was distracted through conversation, then the manoeuvre was surreptitiously repeated and if grasping again occurred (score 10), the examiner said in a peremptory tone 'I have told you not to grasp'; (3) after a short conversation, the manoeuvre was repeated (score 12, if positive); (4) after a few minutes, a final trial was carried out (score 14, if positive).

To sum up, there were seven trials, four given without comment and three after the patient's grasping behaviour had been the subject of negative remarks. The maximum score was 14. If the patient had no, or only mild contralateral paresis, both hands were tested, first the contralateral and then the ipsilateral one In the case of moderate to severe paresis, only the ipsilateral hand was tested.

Groping

After grasping had been tested, the examiner dragged the neurological hammer quickly along the patient's palm and then moved it haphazardly at a distance of about 10 cm from his hand, and slowly moved it away if the patient moved his hand in its direction. The test was discontinued if there was no reaction. If the patient groped for the hammer, a second trial was given and if it produced groping again, the examiner said 'Why are you trying to catch it? . . . I did not ask you to do this'. If a third trial produced groping, the examiner said 'I have told you not to seize it'. A fourth and fifth trial were given at short intervals. At each trial the patient's behaviour was scored 0 (no reaction), 1 (he moved his hand in the direction of the hammer, but desisted before reaching it) or 2 (he grasped the hammer). Maximum score 10.

Grasp reaction

The examiner touched the radial and then the ulnar side of the back of the hand with his stationary fingers. If, after a while, there was no reaction from the patient, the examiner moved the fingers up and down along the same area, maintaining the stimulation if the patient made adjusting movements until a closure response developed. The procedure was repeated three times before considering the result negative.

Foot grasping

A continuous pressure was exerted with the handle of the reflex hammer on the sole in the area of the ball of the foot in three trials, separated by a short interval. Foot grasping was diagnosed if the stimulation produced flexion and adduction of toes associated with curving of the foot.

Location of lesion

The identification of the site of the lesion was based on 9 mm. CT scan slices parallel to the orbitomeatal plane carried out with a CGR ND 8000 CT within a few days of the neurological examination. The Matsui and Hirano's Atlas (1978) was used in the identification of the damaged areas. The figure presented in this paper were derived by tracing the corresponding CT scan slices.

Results

Grasping

Table 1 reports the number and percentage of patients showing the grasp reflex (G+) in each diagnostic category. Of the 26 G+ patients, 24 belonged to categories one and three; namely, they were patients with one or more focal hemispheric lesions, which were sufficiently severe to produce neurological signs. Grasping was never observed (G−) in control patients without brain disease, in patients with a normal neurological examination at the time of testing (epilepsy, or transient/reversible ischaemic attacks), and in patients with subtentorial pathology. One patient with Parkinson's disease and one with subarachnoid haemorrhage without focal damage also displayed grasping, but in the former case the sign disappeared as soon as it was commented upon (score 8) and in the latter case it was present only on the first day of admission.

We shall now consider in more detail the G+ patients with single or multiple lesions.

G+ patients with a single hemispheric lesion (n = 14)

The data of these 14 patients are summarized in Table 2. With the exception of two patients (Cases 39, 133), who scored 8 and 6, respectively, grasping persisted in 12 patients after the first admonition ('why are you grasping?') and in 11 also after the second one ('I have told you not to grasp').

TABLE 2 GRASPING IN PATIENTS WITH UNILATERAL LESIONS

Case	*Hands tested*	*Score*	*Other grasping phenomena (score)*	*Etiology*
1	1	14	Groping (6) grasp reaction	V
2	2	14B		N
10	1	14		V
13	2	10C		N
39	2	8B		V
49	2	10B		N
52	1	14		V
64	1	14	Groping (4)	V
65	2	14B		N
75	2	14B		V
99	2	12B		V
104	2	14B		V
133	1	6		V
134	2	14I		V

B = both hands; C = contralateral hand, I = ipsilateral hand; V = vascular lesion; N = neoplastic lesion. Patients 1, 10, 52, 64, 133 were tested in the ipsilateral hand only, because of severe contralateral paresis.

Both hands could be tested in nine G+ patients: seven of them showed bilateral grasping, while in one patient it was confined to the hand contralateral and in one to the hand ipsilateral to the side of lesion. Only the ipsilateral hand was testable in five patients, because of severe contralateral paresis.

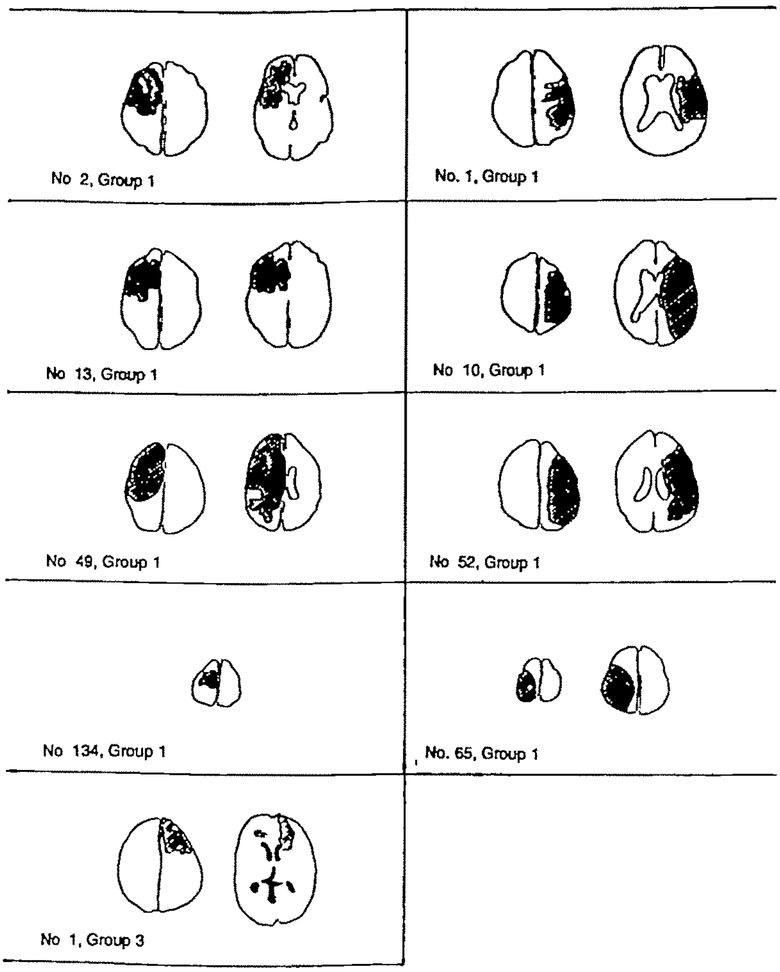
Based on CT scan findings (or on neurological examination in the four cases with or without negative CT scan), five patients were diagnosed with left brain damage and nine with right brain damage.

Of the 14 G+ patients, one died before a CT scan could be carried out and three had a negative CT scan. The remaining 10 patients were grouped into three categories, according to whether the lesion involved the medial frontal lobe, the lateral frontal lobe or was mainly centred around the deep nuclei. If the lesion was both medial and lateral, the patient was categorized in the medial group.

Medial cortical lesion (n = 4). In one of the four patients (Case 134) belonging to this group, the supplementary motor area (SMA) alone was damaged. In a second patient (Case 13) the lesion involved the SMA as well as the gyrus cinguli (GC). Both structures were encroached upon by the oedema surrounding a tumour, more laterally or inferiorly located in the last two cases (Cases 2, 49) (*see* the left half of Fig. 1).

Lateral cortical lesions (n = 4). Two patients (Cases 10, 52) had a large middle cerebral artery (MCA) infarct, which encroached upon the precentral gyrus (M1), the superior frontal (SF) and the middle frontal (MF) gryus; the third (Case 1) had a temporoparietal infarct extending to M1 and SF, but not MF; the fourth (Case 65) had a meningioma covering the parietotemporal cortex and reaching anteriorly to MF (*see* the right half of Fig. 1).

Deep nuclei (n = 2). One patient (Case 39) had a lenticulo-insular haematoma and a second (Case 133) a haematoma extending from the temporal and supramarginal cortex to the posterior paraventricular white matter (PVWM), the putamen and the posterior part of internal capsule (CIp). The white matter of the


No 2, Group 1

No. 1, Group 1

No 13, Group 1

No 10, Group 1

No 49, Group 1

No 52, Group 1

No 134, Group 1

No. 65, Group 1

No 1, Group 3

FIG. 1. CT slices showing the extent of lesions in G+ patients of Study 1 with medial (left half of the figure) and lateral (right half) cortical damage. The lowest figure of the left half corresponds to a patient with a major lesion in the right medial frontal area and a minor lesion in the left white matter of MF (*see text*) Black = hyperdense areas, dashed = hypodense areas

frontal lobe was not damaged. Both patients had a relatively mild form of grasping, which disappeared as soon as the patient was warned (scores 6 and 8, respectively).

G+ patients with multiple hemispheric lesions (n = 10)

Grasping was present in 10 patients out of the 53 (19.9%) belonging to this group. Nine of the patients did not respond to the attempts to induce remission (score 14). In all patients both hands could be tested and grasping was detected bilaterally. The etiology was always vascular.

CT scan data were not available for one patient (who could not be examined because of lack of cooperation) and were negative in two patients. Among the seven G+ patients with positive CT findings, one (Case 1) had a lesion produced by a gunshot wound located in the left medial frontal lobe and involving the SMA (*see* the bottom picture of the left half of Fig. 1). The presence of a small lesion in the white matter of MF in the right hemisphere prevented the assignment of this patient to group one The remainder had lacunae in the deep nuclei and/or the PVWM and in one case (Case 4) there was intense leucoaraiosis around the frontal horns.

Patients with unilateral lesion involving the frontal lobe, but without grasping

Among the G− patients with hemispheric lesions, 25 had damage which extended to the frontal lobe, based on CT scan findings. The lesion was directly located in the SMA in just one case (Case 129, an arterovenous malformation), while in another three cases (Cases 11, 66, 128) this area was involved by oedema from a tumour of the polar part of the SF and MF gyri.

One patient (Case 132) had a large subdural haematoma covering the lateral mantle, one (Case 92) an intracerebral haematoma in the basal frontal white matter and two (Cases 86, 98) an infarct in the frontal white matter bordering the frontal horn and in front of it, respectively. All of the remainder (i.e. 17 patients) had a lesion of M1 and 11 also of the premotor cortex [SF, MF, inferior frontal (IF), alone or in combination].

In this negative group, 11 patients had left brain damage and 14 right brain damage.

Minor manifestations of grasping

Twenty-five patients had a score of 1−3 on the first three trials in at least one hand. They were not tested further, but notice was taken of their clinical features. Six belonged to Group 1 (4%), five to Group 2 (9%), four to Group 3 (7%), four to Group 4 (29%), one to Group 6 (3%), one to Group 8 (3%) and four to Group 9 (3%). Of the 10 patients for whom CT scan documentation was available, none showed a frontal lesion.

Other grasping phenomena

Groping was observed in four G+ patients, two belonging to Group 1 (Cases 1, 64) and two to Group 3 (Cases 1, 9). In the patients of the former group the behaviour disappeared after the first and the second warning, respectively; in those of the latter group it persisted unmodified, despite warnings.

Instinctive grasp reaction was shown by just one G+ patient belonging to Group 1 (Case 1).

Foot grasping was never observed.

Conclusions from Study 1

When the diagnosis of grasping was based on repeated and clear-cut manifestations of hand flexion around the examiner's fingers, the sign was found in 26 of the 340 patients (8%) with cerebral disease and in none of the 151 patients without disease involving the brain. In the former group, grasping was almost always associated with focal hemispheric damage, with two exceptions: a parkinsonian patient and a patient with subarachnoid haemorrhage, showing the phenomenon in a fleeting way. Cases with positive CT scan findings afforded the opportunity to specify better the intrahemispheric locus of the lesion responsible for grasping and showed that there are essentially two conditions in which it appears: frontal damage and multiple lesions involving the deep nuclei. Disease confined to the cortical and subcortical retrorolandic areas never resulted in grasping: there were at least 29 patients with focal lesions restricted to this region and none displayed grasping.

The small number of G+ cases with a well-documented lesion does not permit us to go very far in the identification of the frontal lobe areas or deep structures crucially implicated in the pathophysiology of grasping, but at least a few provisional conclusions can be ventured. First, within the frontal lobe, grasping appears to be associated with damage either to the medial cortex in front of the motor strip, or to the motor and/or premotor areas on the lateral surface, possibly centred around MF. This statement must be conditional, however, owing to observation that damage to neither area was *consistently* linked with grasping, particularly in the case of the lateral cortex, where there was a substantial number of negative cases. There were 11 negative cases among the 15 patients with lateral damage and four among those with medial damage. Deep lesions were too few to warrant any reliable inference about localization.

STUDY 2

Since Study 1 confirmed the relevance of frontal damage to grasping, but yielded too few cases to permit a reliable estimate of the areas responsible for the symptom, we undertook a second study with the aim of increasing the number of patients in order to provide an answer to this question. To this end we focused on patients who met either of the following requirements: evidence of frontal lobe pathology provided by CT scan or presence of grasping. It must be said, however, that the search for grasping was not so systematic as in Study 1 and was generally carried out on those patients for whom there was at least a suspicion of frontal lobe damage. This approach resulted in the selection of 44 new patients, most of whom had evidence of damage to the frontal lobe. Twenty-six suffered from vascular disease, 16 from tumour, one from an abscess and one from trauma. Ten patients had bilateral lesions, 20 had a left hemisphere lesion and 14 had a right hemisphere lesion.

Grasping was tested following the procedure described in Study 1.

Results

Grasping

Grasping was found in 24 patients who scored 14, and in two patients who scored 10, i.e. they interrupted grasping when explicitly warned to refrain from it (Table 3). In 20 patients grasping was bilateral, in two it was confined to the contralateral hand, and in the remaining four only the ipsilateral hand could be tested because the contralateral one was severely paretic. Grasping was present in 11 patients with left brain damage (55%), in 10 with right brain damage (71%) and in five with bilateral damage (50%). Eighteen patients did not show grasping.

As in Study 1, patients were classified in three groups: medial cortical lesions, lateral cortical lesions and deep nuclei lesions. Figure 2 shows the location of damage in the medial and lateral cases.

Medial lesions. The lesion affected the medial regions of the hemisphere in 24 patients. Seventeen of them (71%) were G+ and seven were G− Among G+ patients, 14 had cortical damage in front of the Rolandic fissure, two (Cases 22, 23) had a single infarct in the subjacent white matter, just in front of the anterior wall of the frontal horn, and one (Case 21) had a haemorrhage confined to the posterior GC. In the group of 14 patients with medial cortical lesions (Cases 4, 5, 7, 8, 9, 11, 12, 14, 15, 17, 18, 19, 20, 25), nine had damage encroaching upon both SMA and GC (left half of Fig. 3). The right half of Fig. 3 shows the patient with a posterior GC lesion (upper right box) and the two patients with lesions anterior to the frontal horn (two lower right boxes).

In the seven G− patients of the medial group (Cases 2, 4, 5, 8, 15, 16, 17) the lesion always involved the anterior GC, but extended to the SMA in one case (Case 17).

Lateral lesion. Fifteen patients (four G+ and 11 G−) belonged to this group. All of the four G+ patients had a vascular lesion: the first (Case 1) a small infarct of the lower part of M1 and the adjoining posterior part of SF; the second (Case 3) a chronic subdural haematoma spanning the parieto- and temporo-frontal cortex, including MF and SF; the third (Case 16) a large MCA infarct extending to MI, SF and MF, and the fourth (Case 24) a small infarct of MF (Fig. 4).

The frontal lesion of the 11 G− patients involved M1 alone in four cases, extended to the adjoining premotor cortex in four cases and was confined to the premotor cortex in three.

Deep lesion. Of the five patients who showed grasping, but not frontal cortical damage, one (Case 2) had a haematoma of the frontal-parietal periventricular white matter and the lenticular nucleus, one a lacuna (Case 6) of the corona radiata, one (Case 13) an infarct localized to the putamen, the head of the caudate and the anterior limb of the internal capsule, and two bilateral lacunae (Cases 10, 26) in the putamen and both limbs of the internal capsule.

Groping was found in four G+ patients (Cases 7, 8, 12, 22). All had damage to the anterior GC; one had additional damage to the SMA. Groping always affected both hands.

TABLE 3. GRASPING IN PATIENTS OF STUDY 2

Case	*Hands tested*	*Score*	*Other grasping phenomena (score)*	*Etiology*
1	2	14B		V
2	1	14		V
3	1	14		V
4	2	14B		N
5	2	14B		N
6	2	14C		V
7	2	14B	Groping (8)	V
8	2	14B	Groping (1)	N
9	2	14B		N
10	2	14B		V
11	2	14B		N
12	1	14	Groping (8)	V
13	2	14B		V
14	2	14C		V
15	2	10B		V
16	1	10		V
17	2	14B		V
18	2	14B		V
19	2	14B		N
20	2	14B		N
21	2	14B		V
22	2	14B	Groping (8)	V
23	2	14B		V
24	2	14B		V
25	2	14B		V
26	2	14B		V

B = both hands; C = contralateral hand, V = vascular lesion; N = neoplastic lesion
Patients 2, 3, 12, 16 were tested in the ipsilateral hand only, because of severe contralateral paresis.

Conclusions from Study 2

The outcome of Study 2 confirmed to a large extent the findings of Study 1. Thirty-nine patients had a documented lesion of the frontal lobe. Grasping was present in 21 (54%) of them, but showed a much closer association with medial lesions, 17 out of 24 cases (71%), than with lateral lesions, four out of 15 cases (27%). The medial cortical area, consistently damaged in the former group, was located by CT scan at a level lower than that where the SMA is located and corresponded to the anterior part of the GC. The four patients with grasping and a lateral lesion showed involvement of the lateral motor and premotor cortex, the latter being damaged at the level of SF in one case and of MF in two other cases. The lesion of the fourth patient could not be precisely located due to a subdural haematoma.

The occasional participation of deep structure damage in the pathophysiology of grasping was confirmed by the five patients who had the symptom, but not frontal injury. The lesions involved the striatum in four cases and was confined to the corona radiata in the fifth (Case 6).

DISCUSSION

The findings of the present investigation can be summarized as follows: (1) grasping is a sign associated with hemispheric damage; (2) it is never observed with cortical lesions restricted to the retrolandic cortex; (3) its presence points to damage either of the frontal lobe, or of the deep structures—however, although the involvement of these areas is necessary, it is not a sufficient condition for the appearance of the phenomenon,

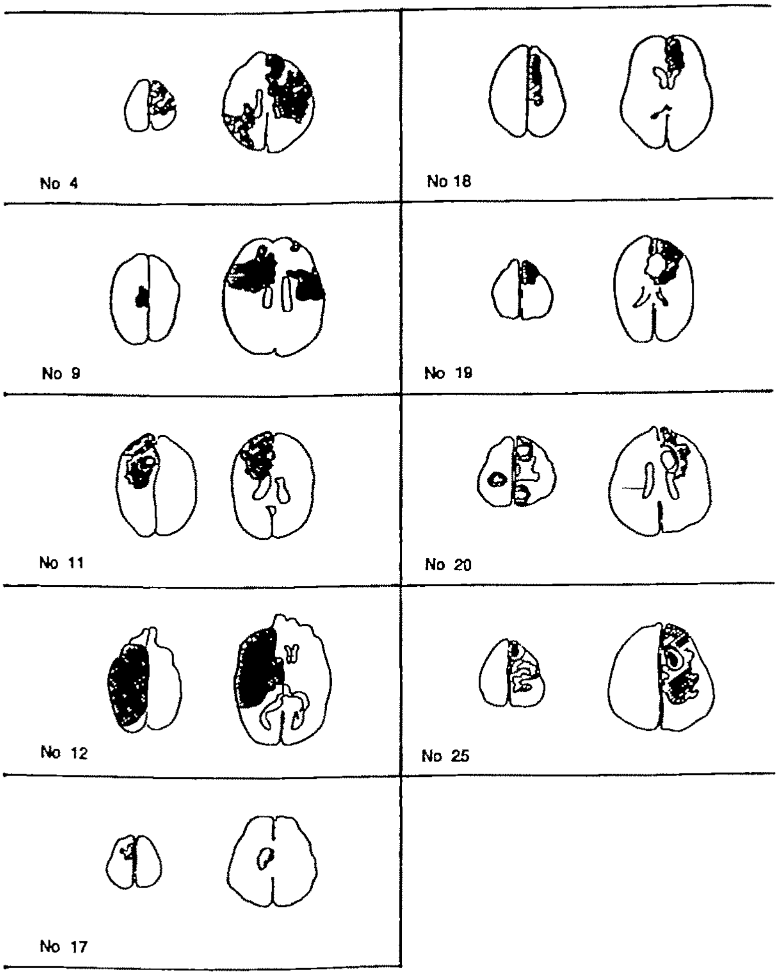


FIG. 2. Tracings of CT scan slices showing the extension of lesion in patients with involvement of both the anterior GC and the SMA. Black = hyperdense areas; dashed = hypodense areas.

in that some patients with frontal damage or deep damage did not show it; (4) unilateral damage often produces bilateral grasping.

Qualitative assessment

Before commenting upon the previous statements in the light of data from clinical and primate studies, we wish to emphasize some behavioural aspects of grasping brought out in this investigation.

Of the 52 patients of the two studies who were considered G+, having scored at least 6 in the first three trials, only six did not attain the maximum score of 14. In the remainder the tendency to grasp was sufficiently robust to override the inhibitory effect that the orientation of attention on hand movements drawn by a previous warning would be

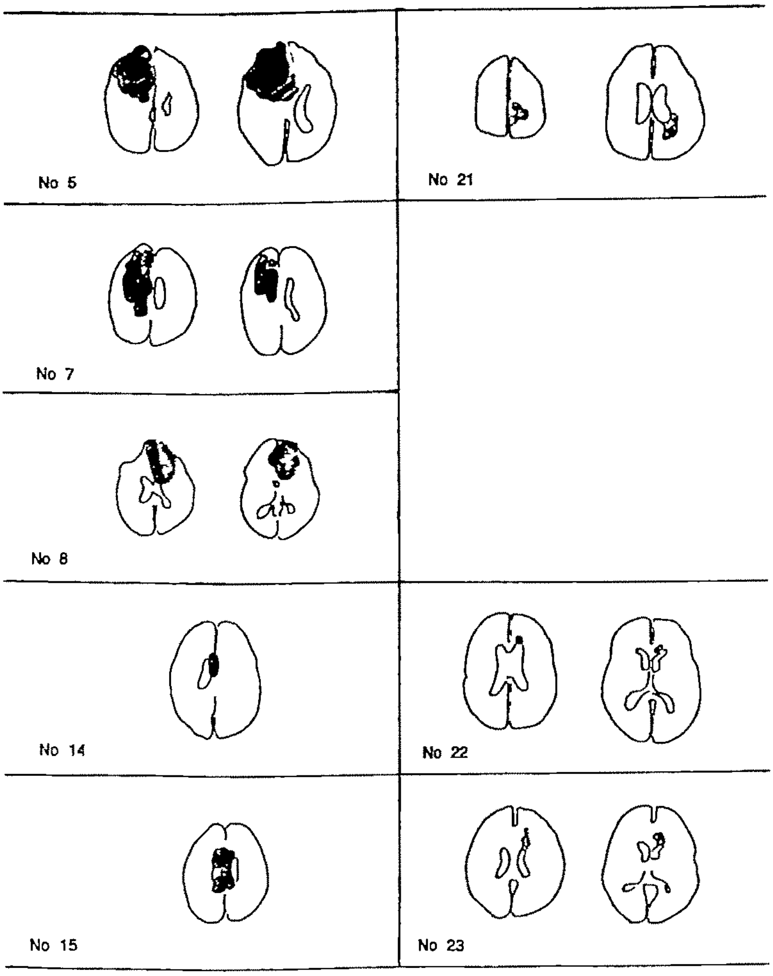


FIG 3. The left half of the figure shows cases with damage confined to the anterior GC The right upper box shows the patient with posterior GC damage, and the two right lower boxes the patients with damage in the white matter anterior to the frontal horn. Black = hyperdense areas, dashed = hypodense areas.

expected to exert. This does not mean that grasping is unmodifiable by will, in the same sense as tendon reflexes are. The majority of patients were able to release the grip when explicitly told to do so and some of them were able to refrain from grasping if the stimulation was made while their eyes were gazing at the palm and, at the same time, they were exhorted not to grasp. The influence of will on grasping, a feature already pointed out by Mayer and Reisch (1928), was at any rate fleeting and did not prevent the patient from returning to the original behaviour after a while, although two patients were observed in a second testing session to interrupt grasping by saying 'Ah, ah . . . you told me not to grasp. I must remember it'. Occasionally, grasping waxed and waned from day to day, or even in the course of the same day. There were, in contrast, a

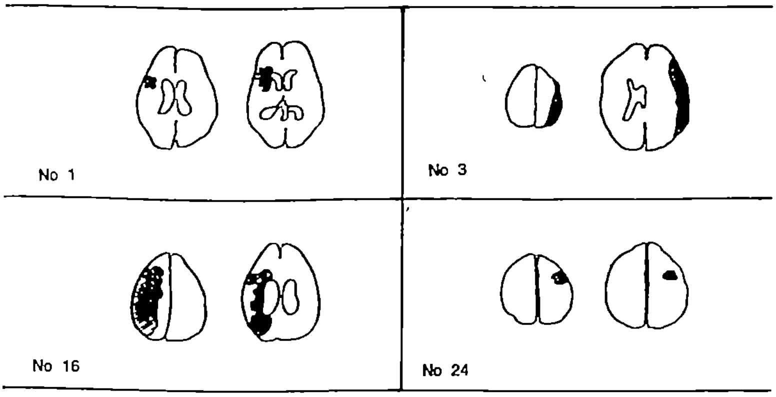


FIG. 4. Tracings of CT scan slices showing the extension of lesion in patients with lateral cortical damage. Black = hyperdense areas, dashed = hypodense areas

few patients who resisted any command and kept on forcibly squeezing any object they happened to touch. Attempts to enquire into the motivations for the grasping behaviour by directly asking the patient, rarely elicited congruous answers. Some patients said 'It is, a sort of instinct', or conceded 'You are right. I must not grasp', but more often they gave silly smilingly justifications: 'It's you who are pulling', 'Otherwise you would fall down', 'Haven't you told me to grasp?' 'Then what am I supposed to do?'

Thus grasping manifests itself with a wide gamut of intensity and the finding that it only rarely shows an irresistible and unmodifiable character would qualify it more as an instinctive behaviour than as a true reflex. These features of grasping were already pointed out by Walshe and Robertson (1933) who questioned the use of the term reflex to designate phenomena in which mental activity played a role and spoke of volitional grasping movements, keeping them separate from reflex tonic grasping, which would be the response to stretching of the flexor muscles of the fingers.

The forced or non-forced nature of grasping has been related to two variables; the hand in which the sign appears and the locus of lesion. Bieber (1940) distinguished forced grasping, strictly contralateral to the lesion and indicative of focal damage, from non-forced grasping, which is bilateral, and devoid of localizing value. The criterion for discriminating between the two phenomena was the ease with which the grasp could be released on command. Hécaen *et al.* (1957) also contrasted the forced grasp reflex with instinctive grasping, defined as a response that can be inhibited or released by explicit warnings. The forced grasp reflex was reported in 13 patients. It was contralateral to the side of lesion in eight cases, bilateral in five, and for eight patients there was evidence that the disease involved the frontal lobe. Instinctive grasping was present in 16 patients; it always affected the hand ipsilateral to the lesion, was associated, with one exception, with damage to the retrorolandic areas and could be accompanied by spontaneous search activity, groping and reduced vigilance. The authors made the interesting remark that instinctive grasping was more frequent after right (12 cases) than left brain damage (four cases), although the lack of information on the samples from which these cases were drawn prevents any firm conclusion. Recently, however, the same hemispheric asymmetry has been reported by Mori and Yamadori (1985), who investigated both the grasp reflex and the instinctive grasp reaction, defined following Seyffarth and Denny-Brown (1948), in a consecutive series of 100 patients hospitalized for unilateral stroke. The grasp reflex was never found, while an instinctive grasp reaction in the hand ipsilateral to lesion was observed in 13 of 45 right brain-damaged patients and in two of 55 left brain-damaged patients, a significant difference favouring the right hemisphere. Most of the cases with an instinctive grasp reaction also showed groping. By far the most frequent lesion was a large infarct in the territory of the middle cerebral artery.

Our data do not tally with those reported by Hécaen *et al.* (1957) and Mori and Yamadori (1985). First, in the majority of cases in which both hands could be tested, the grasp reflex was bilateral. Out of 41 G+ patients submitted to bilateral stimulation in Studies 1 and 2, 37 (90%) showed grasping in both hands (only four had bilateral lesions), three (7%) in the contralateral hand alone (one with bilateral lesion) and one (2%) in the ipsilateral hand only. It is presumed that the nine patients who showed ipsilateral grasping and whose paretic contralateral hand could not be tested would have manifested bilateral grasping, if testable. Secondly, in Study 1 we did not find manifestations of grasping, whether forced or non-forced, associated with damage confined to retrorolandic areas, and just one patient with a posterior location was found in Study 2, but the lesion was in the cingulate gyrus and not in lateral mantle as in the paper of Mori and Yamadori (1985). Thirdly, no significant prevalence of the sign in patients with right brain damage could be brought out. In conclusion, we do not believe that the ease with which the patient releases grasping on command is a feature that contrasts two basically different sets of phenomena, but rather that it simply reflects the severity of the disorder, the same patient having been observed to show forced grasping in the early days of disease and non-forced grasping at a later stage. Mori and Yamadori (1985) do not detail the procedure they followed to elicit the grasp reflex and the instinctive grasp reaction, just saying that they complied with the criteria set out by Seyffarth and Denny-Brown (1948), which, however, are different from those adopted by Hécaen *et al.* (1957) in distinguishing the forced grasp reflex from instinctive grasping. The French authors relied entirely upon the release of grip on command, while Seyffarth and Denny-Brown (1948) described in great detail the different techniques of stimulation used to elicit the two phenomena. While we frequently found the grasp reflex and only exceptionally the instinctive grasp reaction, Mori and Yamadori (1985) frequently found the instinctive grasp reaction and never found the grasp reflex, which is surprising because the latter sign is considered more frequent than the former by Seyffarth and Denny-Brown (1948). One is tempted to suggest that both studies have, in fact, investigated the same phenomenon, though giving it different names, but the different side and site of lesion reported by Mori and Yamadori (1985) in their cases makes the issue difficult to dismiss. Our experience in the present study leads us to suggest that there is little to gain by multiplying the gamut of signs and labels related to grasping, resting on testing procedures that are difficult to differentiate and replicate, and that, apart from the grasp reflex, groping is the only phenomenon that occurs with sufficient frequency to deserve separate consideration, at least for clinical purposes. It was found in four patients of Study 1 and in four of Study 2, always associated with grasping; it was associated with a medial lesion in five cases and multiple deep lesions in two cases. In one case, CT scan was negative.

The anatomical basis of grasping

On the basis of the present data, we conclude that grasping is a pathological sign with a fairly precisely localized origin. Contra to the claim of Seyffarth and Denny-Brown (1948), it was never observed in patients without cerebral damage, provided the criteria for assessing its presence were strict, i.e. three fully-developed consecutive responses in the early testing trials. Negative responses were also obtained from patients with transient neurological deficits, with epilepsy without clinical signs of brain pathology, with a subtentorial lesion and with diffuse degenerative disease, although the number of cases in the last category was too small to permit reaching a definitive conclusion, especially for the later stages of disease, where the sign has been repeatedly reported. By and large, the bulk of evidence supports the conclusion that grasping is associated either with frontal lobe pathology or with damage to the subcortical deep nuclei or pathways. We did not observe it when the lesion was confined to the retrorolandic areas (except for the above-mentioned case of a posterior cingulate lesion), in spite of the fact that positive cases with such a localization are recorded in the literature. It must be stressed, however, that these cases reported in the early literature were all patients affected by tumours and were reported at a time when the diagnosis of an intracranial mass could not take advantage of imaging techniques and was therefore delayed. It is likely that, as the authors reporting these cases suggested, the tumour was accompanied by intracranial hypertension and exerted an effect on the frontal lobe through oedema or compression.

Since the earlier clinical reports of grasping, the attention of neurologists has focused on the medial frontal lobe, but it was in the 1930s that investigators first attempted to substantiate this localization with evidence provided by animal experimentation.

In their pioneer study on the association of the grasp reflex with frontal lesion in monkeys, Richter and Hines (1932) identified in the more dorsal and medial part of the frontal lobe as the region where damage was specifically related to the symptom. This localization was overlooked by Fulton (1934) and Fulton and Kennard (1934), who linked grasping with ablation of area 6, although, according to Wise (1984), they almost certainly included the SMA in the surgical operation. Penfield and Welch (1951) reported that the grasp reflex was not observed when a surgical excision was confined to the lateral frontal cortex, but that it did occur when the lesion extended to the mesial cortex. While its presence following damage to both the lateral and medial parts of area 6 was confirmed by Rushworth and Denny-Brown (1959) and by Goldberger (1972), the question of whether the excision of the SMA alone is sufficient to produce the sign has been the subject of conflicting results, with positives provided by Travis (1955) and Smith *et al.* (1981), and negatives by DeVito and Smith (1959) and Coxe and Landau (1965).

In man, grasping has been found following damage of the non-primary motor cortex (Kennard *et al.*, 1934), but the definition of the extent and location of the cortical damage was imprecise. Foerster (1936) reported negative findings for patients with lesion of area 6ab. No grasping was reported by Laplane *et al.* (1977) in three epileptic patients submitted to circumscribed corticectomy of the SMA, in contrast to Penfield and Jasper (1954) who found the grasp reflex present in comparable cases. More recent studies investigating the clinical correlates of premotor cortex damage have yielded conflicting results on the association of grasping with SMA damage. Derouesné (1973) reported five patients with benign tumours extending to the premotor cortex: two of them involved the SMA and did not show grasping, which was present in one of the three patients with a lateral cortical lesion. Grasping was not mentioned as a presenting sign in the 11 patients with proximal limb paresis and CT documented frontal lesion, mostly vascular, involving the premotor area and sparing the precentral gryus, reported by Freund and Hummelsheim (1985). From the schematic outlines of lesions published in the paper, it would appear that in some cases also the SMA was damaged.

The infarcts of the anterior cerebral artery (ACA) are suitable to assess the relation of grasping to SMA, because this region belongs to its area of supply. The grasp reflex has been reported in patients with an infarct of the left ACA (Critchley, 1930; Rubens, 1975; Alexander and Schmitt, 1980; Goldberg *et al.*, 1981). The patients of Masdeu *et al.* (1978) and Dick *et al.* (1986), however, did not display the grasp reflex. Mostly negative evidence was provided by Bogousslavsky and Regli (1990), who found grasping in only four patients of the 27 with an infarct of the ACA, collected over 7 yrs in the Lausanne prospective stroke registry. Moreover, the authors maintained that the grasp reflex was correlated with involvement of the orbitofrontal cortex, although from the CT scan drawings reported in the article there is insufficient evidence for this claim: a lesion confined to this area was present in just one case (Case 3), was associated with medial frontal damage in two (Cases 16, 17) and was absent in the fourth (Case 23).

It can be concluded that lines of evidence from animal and human studies converge to suggest that lesions of the medial cortex anterior to the precentral gyrus play an important role in causing grasping, but evidence suggesting this association is far from consistent.

Our data are in agreement with these conclusions (Table 4). There were 32 patients in Studies 1 and 2 (one of them with bilateral lesion), in whom the CT scan documentation pointed to the involvement of the medial frontal lobe, and in 21 of them (66%) grasping could be elicited. The brunt of the lesion was in the SMA in 14 cases, but in 12 of them it also extended to the upper part of the GC, which in turn was the only locus of lesions in seven cases. Thus the evidence from the present research suggests that not only the lesion of the SMA, but even more that of the anterior cingulate cortex can be responsible for grasping behaviour.

TABLE 4 INCIDENCE OF GRASPING IN PATIENTS WITH FRONTAL DAMAGE FROM THE TWO STUDIES

	Medial lesion	*Lateral lesion*
Study 1	5/9	4/15
Study 2	16/23	4/15
Total	21/32 (66%)	8/30 (26%)

The pattern of connectivity of the anterior portion of the gyrus cingulate (area 24) suggests that it plays a role in motor control not dissimilar to that exerted by the SMA, of which it is considered an architectonic precursor (Barbas and Pandya, 1987). The two areas are strongly interconnected (Benjamin and Van Hoesen, 1982) and both have direct projections to the spinal cord. In area 24 there are two regions, one located anteriorly in the ventral bank of the cingulate sulcus and the other more posteriorly in both the dorsal and ventral banks, which provide a somatotopically organized route to the cervical and lumbo-sacral spinal cord (Hutchins *et al.*, 1988) similar to that originating from the SMA (Murray and Coulter, 1981), and both areas also project to the pontine grey matter (Vilensky and Van Hoesen, 1981; Jurgens, 1984). Both area 24 and SMA are strongly interconnected with M1 (Muakkassa and Strick, 1979) and both project to the basal ganglia; namely, the head of the caudate and the putamen (Baleydier and Mauguiere, 1980; Pandya *et al.*, 1981; Jurgens, 1984).

Neurophysiological evidence is scanty, but functional involvement of area 24 neurons in the preparation of motor responses is suggested by their firing changes while the monkey is performing a modified differential reinforcement of long latencies tasks (Niki and Watanabe, 1979). Much more abundant are the data concerning the SMA, and the more that is known about it the more it appears as a heterogeneous area with different anatomical and functional specifications (Luppino *et al.*, 1990; Rizzolatti *et al.*, 1990). Thus it is possible that the question of whether it occupies a hierarchically superior position in the control of movement, playing a role in the initiation of internally generated motor sequences (Wise, 1984), or is engaged in the postural control of the proximal limb and trunk muscles (Wiesendanger *et al.*, 1987) may be solved by assigning discrete functions to different subareas. Among these functions there is the inhibitory control on the activity of lower centres, resulting in 'the suppression of relatively automatic responses to sensory stimuli' (Wise, 1985), as in the case for the grasp reflex which is present at birth but is progressively suppressed during the course of brain maturation.

Which route is followed by the inhibitory outflow from the SMA and the contiguous GC can only be a matter of speculation. One can envisage a direct pathway to the cervical cord, or one relaying at the level of pontine nuclei, or the connections with M1 directly or via subcortical loops involving the basal ganglia (Wiesendanger *et al.*, 1975). Schuster and Casper (1930) have suggested that the fibres carrying inhibitory stimuli from the medial frontal cortex travel downwards traversing the white matter anterior and lateral to the frontal horn, whence they run first backwards, then either laterally to the motor cortex or medially to the contralateral hemisphere. In the same region a bundle connecting the cingulum to the caudate nucleus was identified by Yakovlev and Locke (1961) and named stratum subcallosum. Thus the finding that damage to this area was found associated with grasping in two cases can be attributed to massive destruction of the cingulate outflow. The much lower incidence of grasping when the lesion involves the lateral motor cortex or the basal ganglia suggests that the inhibitory stimuli from the medial frontal cortex travel through multiple routes that can compensate each other, and that there is marked interindividual variability in their use.

The prevalence of bilateral over contralateral grasping following damage to one hemisphere found in the present series of patients is at variance with the claim made on the basis of single case reports, but not with the data of group studies; for instance, in a study on self-grasping (the phenomenon whereby the patient grasps with one hand his own contralateral forearm), Ropper (1982) reported 37 consecutive patients who showed bilateral grasping. The finding is not surprising since it is well known that the two SMAs are reciprocally connected (Kunzle, 1978). Evidence that they work in conjunction is provided by the finding (Roland *et al.*, 1980) that in man there is a bilateral increase in regional cerebral blood flow of the SMA during the execution of a unilateral motor sequence. In the monkey, a lesion of one SMA results in the impairment of a bimanual coordination task, which is abolished by callosal section (Brinkman, 1984). It is, therefore, conceivable that damage to one SMA disturbs the activity of the equivalent contralateral area and disrupts the inhibitory control it exerts over the grasp reflex centre.

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DEVELOPMENT OF INTELLIGENCE AND MEMORY IN CHILDREN WITH HEMIPLEGIC CEREBRAL PALSY

THE DELETERIOUS CONSEQUENCES OF EARLY SEIZURES

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SUMMARY

Although substantial data exist regarding the consequences of early lateralized cerebral lesions on intelligence and language ability, little is known about the development of other cognitive functions after such lesions. We examined the development of both verbal and nonverbal memory in 82 hemiplegic children, grouped according to hemispheric side of injury and presence or absence of seizure disorder. The control group consisted of 41 age-matched normal children, most of them siblings of the patients. Measures were obtained of intelligence and of immediate and delayed recall for prose passages, word paired associates and geometric designs. Electrophysiological and neuroradiological measures were available for a majority of the patients.

The scores of the hemiplegic children on the IQ and memory tests did not exhibit the pattern seen in brain-damaged adults, in that the children's deficits showed no relation to hemispheric side of damage. Indeed, early cerebral damage to either hemisphere, even if extensive, resulted in relatively few and mild deficits if the damage was unaccompanied by seizure activity. By contrast, early lateralized lesions that were accompanied by a seizure disorder resulted in both a high incidence and degree of deficit that was unrelated to lesion side.

INTRODUCTION

The incidence of cerebral palsy of perinatal origin is approximately two in 1000 births (Brett, 1983). Of these cerebral palsy cases, approximately one-third have hemiplegia (Paneth and Kiely, 1984; Perlstein and Hood, 1954). The hemispheric brain injury responsible for the hemiplegia is presumed to be a thrombotic, vasospasmic or embolic episode in the middle cerebral and/or the internal carotid artery. Although the etiology of the circulatory event is not well understood, it is believed to occur sometime between the end of the second trimester of pregnancy and the early postnatal period (Brett, 1983; Hagberg and Hagberg, 1984). Typically, the pregnancy and delivery are uneventful, and it is usually not until after the first few months of life that a weakness of one set of limbs is noted. Between 30% and 40% of such hemiplegic cases develop a cerebral seizure disorder (Perlstein and Hood, 1954; Holt, 1961), which commonly responds to anticonvulsant regimes (Holt, 1961) but not invariably (Menkes, 1974).

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In adults, the syndrome most akin to hemiplegic cerebral palsy of perinatal origin also results from cerebro-vascular accidents in the territory of the middle cerebral artery. Such strokes in the left hemisphere of adults often lead not only to hemiplegia but also to impairments in various cognitive functions, including different aspects of language (Brust *et al.*, 1976; Chiarello and Church, 1986; Adams and Victor, 1989), verbal memory (Beauvois and Lhermitte, 1975; Coughlan, 1979; Risse *et al.*,1984; Cappa *et al.*, 1990), calculation ability (Grafman *et al.*, 1982; Rosselli and Ardila, 1989; *see also* Gerstmann's Syndrome, e.g. Roeltgen *et al.*, 1983), reading and writing (Hecaen and Kremin, 1977; Basso *et al.*, 1978) and manual gestures (Kimura and Archibald, 1974). Similarly, hemiplegia following right hemisphere strokes in adults is often accompanied by impairments in visuo-perceptual and spatial functions (Kase, 1988) as well as in nonverbal memory (Boller and De Renzi, 1967).

Examination of the cognitive consequences of early lateralized lesions (i.e. before age 1) has been limited mainly to assessment of IQ and language. IQ studies have yielded variable results (Woods, 1980; Vargha-Khadem *et al.*, 1985; Riva and Cazzaniga, 1986; Aram and Ekelman, 1988) but little evidence of the laterality effect (e.g. selective lowering of verbal IQ after left hemisphere damage and of performance IQ after right) commonly found in adult patients with unilateral lesions.

As for language studies, it is clear that early left hemisphere lesions, unlike those in adulthood, do not cause prolonged dysphasia and lead to at least gross sparing of speech and language (Basser, 1962; Alajouanine and Lhermitte, 1965; Wood and Carey, 1979; Rankin *et al.*, 1981; Vargha-Khadem *et al.*, 1985).

In contrast to the relative abundance of data on the effects of early lateralized lesions on intelligence and language ability, there is a dearth of information on the later development of other cognitive abilities. An important question which has not been addressed is whether the escape of function is specific to verbal IQ and language. Do other aspects of cognitive performance typically subserved by the left hemisphere, such as verbal memory, verbal fluency, reading and writing, and manual gestures show the same pattern of sparing and reorganization? Similarly, what aspects of cognitive performance normally dependent on the right hemisphere are spared or impaired following early right hemisphere lesions?

Our purpose in the present study was to begin to fill this information gap by examining the development of both verbal and nonverbal memory in hemiplegic children with and without seizures.

METHODS

Subjects

Forty-two patients with left hemisphere lesions, 40 patients with right hemisphere lesions, and 41 normal control subjects were studied. The patients had all presented as children with neurological problems to the neurology departments of two paediatric hospitals, either for initial diagnosis or routine follow-up management. The criterion for the selection of patients was the existence of a measurable degree of hemiparesis, independent of severity, resulting from a unilateral brain lesion sustained pre- or perinatally. The unilateral nature of the injury was determined by neurological examination, electroencephalograms (EEG) and computed tomography (CT) or magnetic resonance imaging (MRI). Patients with bilateral involvement and those with indications of other confounding disorders were excluded from the sample.

The perinatal origin of the brain injury was determined by a neurologist on the basis of (1) a normal course of pregnancy, delivery and postpartum period; (2) a unilateral motor, coordination or body size deficit as documented by a physician during the first 6 mths of life; (3) an abnormally early demonstration of hand preference (i.e. preferential use of one hand and neglect of the other). Patients were excluded if there was evidence that the hemiparesis followed a late postnatal episode (i.e. later than 6 mths of age) (Michaelis *et al.*, 1980; Cohen and Duffner, 1981).

The patient groups with left or right hemisphere lesions were further subdivided on the basis of presence or absence of clinical seizures of cerebral origin, exclusive of febrile seizures during the first 5 yrs of life. (Only a small minority had started their first seizure after the age of 3 yrs.) Also excluded were patients with uncontrolled seizure disorders, i.e. those seizing frequently on a daily basis and/or those who had suffered episodes of status epilepticus. (Patients with seizures occurring on a daily basis were excluded to avoid bias from the obfuscating effect of a recent attack, whereas patients with episodes of status epilepticus were excluded because of the possibility of bilateral hemispheric involvement and insult as a result of such episodes.) Finally, patients with IQ scores below 70 were excluded from the sample. The latter restriction resulted in the elimination of one subject only. The resulting groups were designated LNS (n = 28) for left hemisphere lesions with no seizure disorder, LS (n = 14) for left hemisphere lesions with seizure disorder, RNS (n = 24) for right hemisphere lesions with no seizure disorder; and RS (n = 16) for right hemisphere lesions with seizure disorder. All patients in the seizure groups were on anticonvulsant drug therapy. Before psychological testing, the adequacy of the blood levels for anticonvulsants was verified for all patients except two. In some cases, the medication eliminated all seizures, but in others the seizures continued to occur as frequently as one per week.

The normal control group, designated NC, consisted of 23 siblings of patients, plus 18 subjects selected from a larger pool who were considered comparable with the patients with respect to age, IQ and socio-economic status.

All subjects were of normal intelligence with a range from dull to bright normal, and none was clinically dysphasic. Table 1 shows the number of subjects in each group, and their mean full-scale, verbal and performance IQs, as well as their age at time of testing. In view of the wide age range (6–21 yrs), the groups were further subdivided by age, with the dividing point placed at 12.0 yrs, for statistical analysis.

TABLE 1 AGE AND IQ SCORES OF SUBJECT GROUPS MEANS AND STANDARD DEVIATIONS

		Age (yrs/mths)		*IQs*					
				Full scale		*Verbal*		*Performance*	
Group	*n*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
LNS	28	12.9	3.7	99.8	14.0	101.3	16.1	98.6	14.0
RNS	24	11.3	3.5	100.7	16.3	103.4	16.5	97.9	15.3
LS	14	11.8	2.6	83.7	13.5	86.2	13.4	83.9	12.7
RS	16	11.6	3.6	89.3	12.0	90.1	14.0	90.3	12.4
NC	41	11.8	3.3	107.2	11.1	104.3	12.0	109.6	12.0

Materials and procedures

Psychological measures

Intelligence was measured with the Wechsler Intelligence Scale for Children—Revised (Wechsler, 1976). The test was administered in full, to provide measures of both verbal and performance intelligence (VIQ, PIQ).

Memory was measured with the Wechsler Memory Scale (WMS), Form I (Wechsler and Stone, 1945). Age corrections similar to those employed for individuals over the age of 20 yrs were used, as suggested by Taylor (personal communication, 1981). Three subtests were selected to provide measures of both immediate and delayed recall, as follows:

(1) *Logical memory.* For children over the age of 12 yrs, the two standard Wechsler stories constituting the Logical Memory subtest (Form I) were used, containing 23 and 22 units of information, respectively. For children below the age of 12 yrs, two children's stories developed by Taylor (Kimura and McGlone, 1979) were substituted for the standard Wechsler stories. Each of these contained 18 units of information. Whichever set was used, recall of each story was obtained immediately after its presentation and an average score calculated for the two stories. Following a 90 min interval filled with other tasks, delayed recall of each story was obtained and an average score again calculated (Milner, 1975)

(2) *Paired associate learning.* This subtest was administered as described in the WMS manual and scored for immediate recall after each of the three presentations of the 10 paired associates. The set of 10 pairs consists of six pairs of related items (e.g. up-down) and four pairs of unrelated items (e.g. cabbage-pen). These two subsets were scored separately. Recall was also measured after a 90 min filled delay. Delayed recall was scored out of 10.

(3) *Visual reproduction.* The immediate reproduction of geometric designs was scored as described in the WMS manual. In addition, following 40 min filled with interpolated tasks, subjects were again asked to draw the geometric designs from memory (Milner, 1975).

Neurological measure

To quantify the severity of the hemiplegia, all subjects were administered a calibrated test of hand grip strength, measured with a Kiddie Hand Dynamometer. Three readings of grip strength (in kilograms) were obtained from each hand, and the mean difference in power between the two hands was calculated. The hand ipsilateral to the hemispheric side of lesion was always tested first.

To quantify severity of motor loss, results were rated in the following way. The difference in power between the two hands was calculated on the basis of norms for each hand at each age level (Lafayette Co., 1989). A difference that was more than 2 SDs above the normal differential was rated as severe motor loss (1), 1.51 to 2 SDs above normal as moderate loss (2), 1 to 1.5 SDs above normal as mild loss (3) and less than 1 SD above normal as normal (4).

Neuroradiological measure

Computed tomography scans were obtained for 35 patients and the abnormalities rated according to the following five-point scale (Vargha-Khadem *et al.*, 1985): (1) moderate to marked ventricular dilation and gross loss of substance seen on three or more cuts; (2) moderate to marked ventricular dilation with minimal to moderate loss of brain substance seen on fewer than three cuts; (3) moderate cerebral atrophy indicated by moderate to marked ventricular dilation seen on three or more cuts; (4) minimal hemisphere atrophy indicated by minimal ventricular dilation—asymmetry seen on fewer than three cuts; (5) normal.

Magnetic Resonance Imaging was performed on 12 other patients. The same five-point rating scale designed for the CT scans was adjusted to allow assessment of the abnormalities on the MRIs.

Patients with CT or MRI ratings of 1 or 2 all had porencephalic cysts.

Electrophysiological measure

Eelectroencephalography recordings were obtained for 58 of the patients. Each recording was analysed and rated by an electrophysiologist for nature of abnormality (diffuse, focal, paroxysmal), type of epileptiform activity, severity, condition during which abnormality occurred and changes relative to previous recordings. Results of these analyses were then compiled and rated according to a four-point severity scale ranging from 1 (severe) to 4 (normal). For purposes of correlations with psychological analyses, the ratings used were those for the EEG recording closest to the time of psychological testing.

RESULTS

Psychological

Statistical analyses of the psychological test results were performed in two steps. In the first step, the normal control group was excluded. The effects of hemispheric side of lesion, presence or absence of seizures, age at testing, and test condition were evaluated on each of the tests (FSIQ, VIQ, PIQ, MQ, logical memory: immediate recall; logical

memory: delayed recall; visual reproduction: immediate recall; visual reproduction: delayed recall; paired associate learning: related pairs; paired associate learning: unrelated pairs; paired associate learning: third trial; paired associate learning: delayed recall).

In no case was the effect of hemispheric side of lesion found to be significant (*see* Table 2 and Appendix). The scores for this variable were therefore collapsed and a new set of analyses of variance, this time *including* the normal control group, were then performed on each test. Here the factors consisted of: groups [seizures (S), nonseizures (NS), and normal controls (NC)]. Age (12 yrs or younger and older than 12 yrs) and test condition. *Post-hoc* testing was carried out using the Newman-Keuls procedure (Winer, 1971), and paired comparisons were carried out using *t* tests. Only statistically significant results are reported below.

TABLE 2 FIRST SET OF ANALYSES OF VARIANCE

Variables	*Significant effects*	*F*	*d.f.*	*P*
MQ (younger group)	Seizure	13.95	1,34	<0.001
Full-scale IQ	Seizure	17.65	1,78	<0.001
Performance IQ and Verbal IQ	Seizure	17.47	1,74	<0.001
Taylor stories	Seizure	5.28	1,38	0.027
	Condition	31.34	1,38	<0.001
Adult stories	Condition	26.22	1,36	<0.001
Paired associate learning Related pairs	Seizure	12.80	1,74	<0.001
	Age	26.29	1,74	<0.001
	Seizure×age	6.13	1,74	0.016
	Condition	66.28	2,148	<0.001
	Seizure×condition	5.23	2,148	0.006
	Age×condition	3.54	2,148	0.032
Paired associate learning Unrelated pairs	Seizure	13.58	1,74	<0.001
	Age	4.40	1,74	0.039
	Condition	105.20	2,148	<0.001
Paired associate learning Trial 3 and delayed recall	Seizure	17.47	1,74	<0.001
	Age	7.42	1,74	0.008
Visual reproduction	Seizure	7.98	1,74	0.006
	Age	18.53	1,74	<0.001
	Condition	115 59	1,74	<0.001

Full-scale IQ. The ANOVA for full-scale IQ yielded a significant main effect of group ($F = 25.65$; d.f. 2,112; $P < 0.001$). *Post-hoc* testing revealed that the S group scored below both the NS and NC groups, and NS scored below NC.

Verbal IQ versus performance IQ (Fig. 1). This comparison revealed a significant main effect of groups ($F = 22.35$; d.f. 2,116; $P < 0.001$) and a significant interaction of group by condition ($F = 5.02$; d.f. 4,116; $P = 0.008$). *Post-hoc* comparisons showed that the S group scored below both the NS and NC groups on both VIQ and PIQ. The NS group, by contrast, scored below the NC group on PIQ only.

Paired comparisons between conditions showed a difference only for the NC group, whose PIQ was significantly higher than its VIQ ($t = 2.43$; d.f. 19; $P = 0.02$). Figure 1 illustrates this interaction of group by condition.

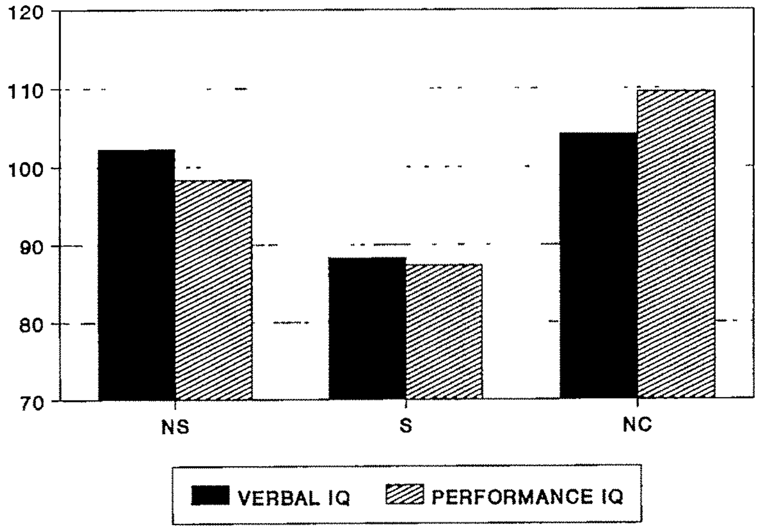

FIG. 1. Verbal IQ and performance IQ

Memory quotient (MQ). Separate analyses were carried out for the subjects aged 12 yrs or younger who had the children stories (Taylor) and the subjects aged more than 12 yrs, who had adult stories (Wechsler).

For the MQ for age $\leq$ 12 yrs, the ANOVA yielded significant group differences (F = 12.32; d.f. 2,56; $P < 0.001$). *Post-hoc* testing indicated that the S group (average = 73.1) scored below both the NS and NC groups (average = 92.6 and 95.0, respectively).

For the MQ for age $>$12 yrs, again the ANOVA showed a significant group effect (F = 8.1; d.f. 2,58; $P < 0.001$). Here the Newman-Keuls analysis indicated that both the NS and S groups (average = 97.6 and 89.4, respectively) scored below the NC group (average = 108.4).

Logical memory: immediate versus delayed recall (Fig. 2). Again the two age groups, presented with different stories, were treated separately. The ANOVA for the younger group, given the Taylor stories, showed a significant main effect for group (F = 7.48; d.f. 3,58; $P = 0.001$). *Post-hoc* testing indicated lower scores for the S group than for either the NC or NS groups, which did not differ significantly from each other. The ANOVAs for both age groups showed a significant effect of conditions (F = 39.5; d.f. 1,58; $P < 0.001$, and F = 42.35; d.f. 1,57; $P < 0.001$ for the younger and older groups, respectively) indicating lower delayed than immediate recall scores for all groups.

Paired associate learning—related pairs (Fig. 3). The two-way ANOVA indicated significant main effects for group (F = 13.19; d.f. 2,117; $P < 0.001$), age (F = 32.22; d.f. 1,117; $P < 0.001$), trials (F = 89.75; d.f. 2,234; $P < 0.001$) and the following interactions: age×group (F = 5.00; d.f. 2,117; $P < 0.008$), group×trials (F = 5.42; d.f. 4,234; $P < 0.001$) and age×trials (F = 7.99; d.f. 2,234; $P < 0.001$). All groups showed increasingly higher scores over the three trials. *Post-hoc* testing revealed that in the younger subpopulation the S group scored below the NC and NS groups, which

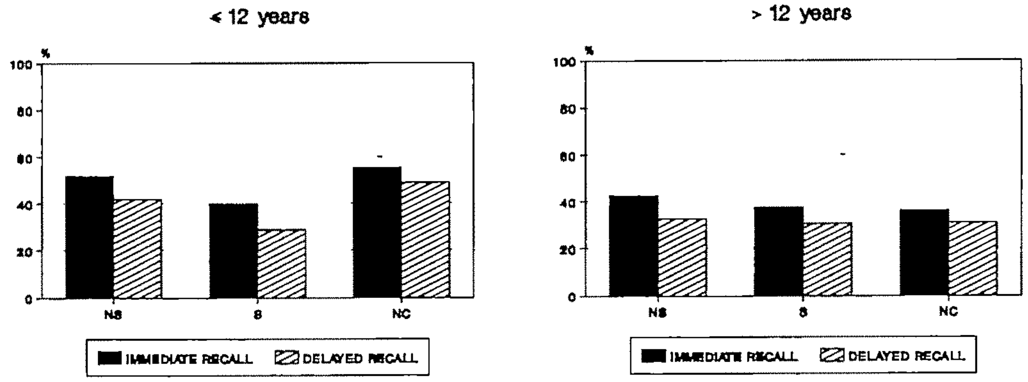

FIG. 2. Logical memory.

did not differ from each other. In the older subpopulation a significant group difference was found only on the first trial, and only between the S and NC groups.

Paired associate learning—unrelated pairs (Fig. 3). The ANOVA revealed significant main effects for group (F = 18.75; d.f. 2,117; $P < 0.001$), age (F = 3.99; d.f. 1,117; $P < 0.048$) and trials (F = 150.65; d.f. 2,234; $P < 0.001$). Again, all groups showed increasingly higher scores over the three trials, and the younger subjects scored below the older. Across all trials, the means of the S group were below those of both the NS and NC groups. In addition, the mean of the NS group was below that of the NC group.

Paired associate learning—third trial versus delayed recall (Fig. 4). Results of the two-way ANOVA indicated significant main effects of group (F = 15.74; d.f. 2,117; $P < 0.001$), age (F = 6.11; d.f. 1,117; $P = 0.015$) and condition (F = 4.81; d.f. 1,117; $P = 0.003$). Across both the trials and recall conditions, the mean scores of the S group were below those of the NS and NC groups, and the scores of the younger subjects were below those of the older subjects (not graphed). Finally, across all subgroups, there was significant loss of learned information during the delay interval.

Visual reproduction—immediate versus delayed recall (Fig. 5). The ANOVA yielded a significant effect of group only (F = 17.48; d.f. 2,117; $P < 0.001$). *Post-hoc* testing indicated that the mean recall scores of the S group were below those of the NS and NC groups, while the mean of the NS group was below that of the NC group. The factors of age and condition were also significant (F = 183.91; d.f. 1,117; $P < 0.001$), indicating that recall of older subjects was higher than that of younger subjects (not graphed), and immediate recall was higher than delayed recall.

Neurological

For these and other rating scores (neuroradiological and EEG), nonparametric analyses of variance (Kruskall-Wallis) were used.

The first analysis examined whether the seizure and nonseizure patient groups differed in the severity of hemiplegia, as reflected in the difference in the dynamometer ratings of the two hands (Table 3). Results of this analysis showed no significant differences ($\chi^2 = 1.82$; $P < 0.176$).

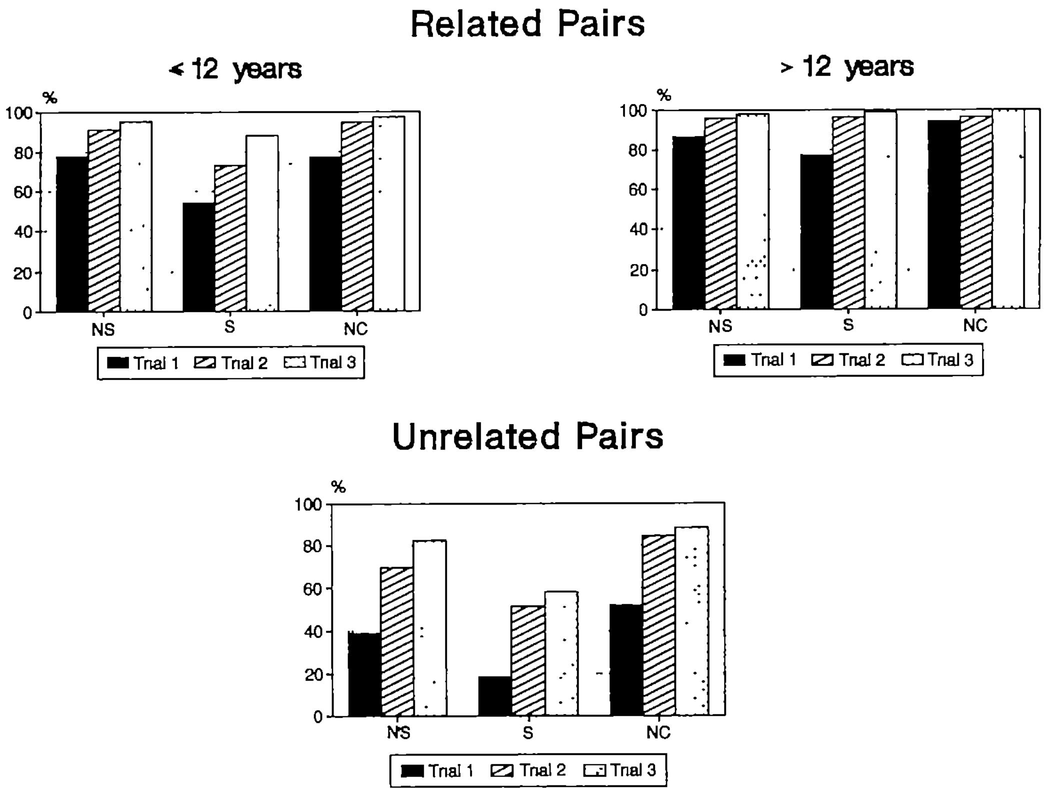

FIG. 3. Paired associate learning.

Neuroradiological

Examination of scans indicated that approximately one-half of the patient population had porencephalic cysts and variable extents of loss of brain structure, whereas the other half suffered from variable extents of diffuse hemispheric atrophy.

The first comparison examined whether the seizure and nonseizure patient groups differed with respect to severity of neuroradiological abnormality. The results indicated that the NS group (average = 3.22, SD = 1.22) had less severe neuropathology ($\chi^2 = 15.5$. $P = 0.002$) than the S group (average = 1.70, SD = 1.13).

Analyses were then performed to determine whether severity of structural abnormality influenced performance on the psychological tests. The comparison was between subjects with ratings of 1 or 2 (subgroups with severe abnormality, n = 24) and those with ratings of 3, 4 or 5 (subgroup with mild abnormality, n = 23). Results indicated a significant difference on the measure of performance IQ only ($\chi^2 = 8.4$; $P < 0.003$), the severe subgroup (average = 89.2; SD = 13.3) scoring below the mild subgroup (average = 101.8; SD = 13.3). The same result was obtained when comparisons were made between the scores of the two nonseizure subgroups (severe S = 8; mild S = 19). Only performance IQ differed significantly ($\chi^2 = 4.20$; $P < 0.04$), the severe

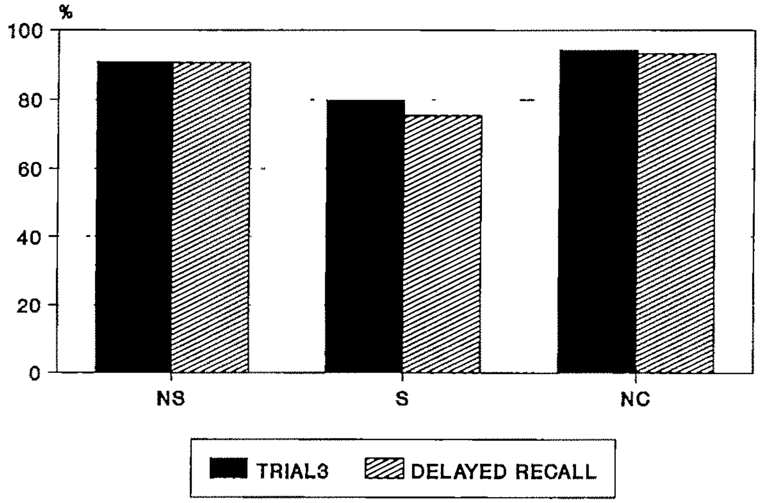

FIG. 4. Paired associate learning: third trial and delayed recall.

subgroup (average = 93.3; SD = 11.2) scoring lower than the mild subgroup (average = 104.2; SD = 11.8). There were no significant differences between the two seizure subgroups on any measure.

The psychological effects of loss of brain substance versus the effects of seizures were then investigated by contrasting the test results of the NS-severe subgroup (n = 8) with those of the S-mild subgroup (n = 4). Table 4 lists the statistically significant comparisons along with the relevant means and standard deviations. In each comparison, the mean of the S-mild subgroup was lower than that of the NS-severe subgroup.

Electrophysiological. As in the case of the neuroradiological ratings, the comparison of the EEG ratings of the patient groups showed statistically significant differences ($\chi^2 = 17.6$, $P < 0.0005$), with the mean ratings of the two nonseizure groups (LNS, average = 2.9, SD = 1.1; RNS, average = 2.9, SD = 0.8) being less abnormal than those of the two seizure groups (LS, average = 1.6, SD = 0.8; RS, average = 1.9, SD = 0.8).

The patients were then divided into two subgroups on the basis of severity of EEG ratings (severe, n = 34; mild, n = 24) and analyses performed on each of the dependent measures. Significant differences were obtained on five variables; these are listed in Table 5 along with the relevant means and standard deviations.

Within the NS group, comparisons between the severe and mild subgroups indicated a significant difference only on the paired associates/delayed recall measure ($\chi^2 = 4.27$, $P < 0.05$), the mean of the severe subgroup (average = 8.7; SD = 1.4) falling below that of the mild subgroup (average = 9.4; SD = 1.4). No differences were found between the S subgroups on any measure. Similarly, contrasts between the psychological effects of seizures (S-mild, n = 3) versus EEG abnormality (NS-severe, n = 13) failed to yield significant differences.

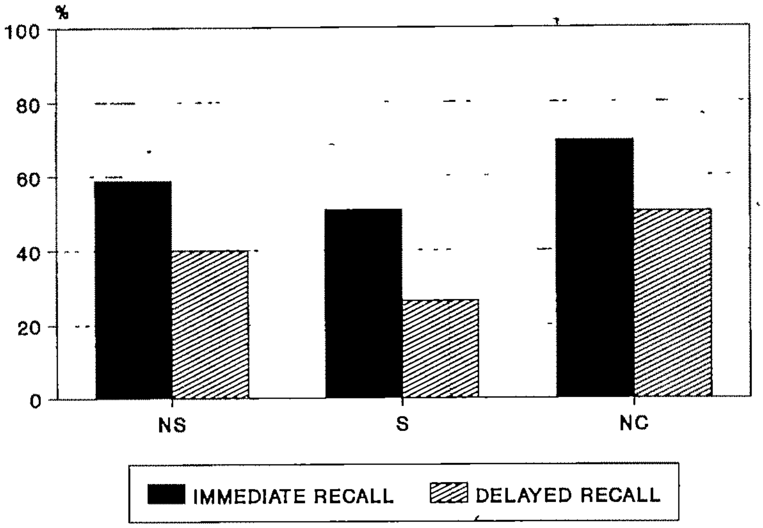

FIG. 5 Visual reproduction.

TABLE 3. DYNAMOMETER READINGS (KG)

	Ipsilateral		*Contralateral*		*Differential*	
Group	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
LNS	18.72	8.0	12.14	7.8	6.59	5.3
RNS	19.44	7.8	9.36	6.3	10.08	7.4
LS	18.45	9.2	8.27	7.2	10.18	4.3
RS	19.50	7.5	11.45	10.5	8.06	5.4

TABLE 4 EFFECTS OF LESION SIZE VERSUS SEIZURES

Variable	*Subgroup*	*Mean*	*SD*	χ^2	*P*
Verbal IQ	NS-severe	105.25	9.8	7.41	0.007
	S-mild	86.50	4.0		
MQ	NS-severe	97.50	12.5	5.69	0.017
	S-mild	76.25	11.0		
Paired associate learning: third trial	NS-severe	9.63	0.5	8.19	0.004
	S-mild	7.75	0.5		

DISCUSSION

The foregoing analysis yielded two major findings, neither of which could easily have been predicted on the basis of previous data. First, children with hemiplegia resulting from perinatal damage to the left or right cerebral hemisphere, while showing substantial impairments on various IQ and MQ measures, failed to exhibit any of the differences in impairment related to side of hemispheric injury that are known to follow similarly

TABLE 5 EFFECTS OF EEG ABNORMALITY

Variable	*Subgroup*	*Mean*	*SD*	χ^2	*P*
Verbal IQ	Severe	92.44	14.1	5.32	0.021
	Mild	102.54	15.9		
Full-scale IQ	Severe	91.67	13.6	4.32	0.038
	Mild	100.87	14.4		
MQ	Severe	82.21	15.7	8.84	0.003
	Mild	96.29	15.3		
Paired associate learning delayed recall	Severe	7.88	1.6	15.12	0.0001
	Mild	9.29	1.5		
Paired associate learning third trial	Severe	8.3	1.5	6.75	0.009
	Mild	9.1	1.4		

located lateralized lesions in adults (Kase, 1988). Secondly, the incidence and degree of deficit were highly related to the presence of seizures and/or severe EEG abnormality; lateralized cerebral damage alone, even if it was extensive, resulted in relatively few and mild deficits provided the damage was not accompanied by seizure activity of severe EEG abnormality.

The absence of laterality effects in the hemiplegic children is probably to be accounted for in the following way. If lateralized damage leads to only relatively mild deficits, as it did in the nonseizure group, differences between the effects of left- and right-sided lesions are likely to emerge only infrequently. In fact, only four tests revealed any losses in the nonseizure patients (one verbal measure, namely unrelated paired associates; and three nonverbal measures, namely performance IQ, and immediate and delayed visual reproduction), and in each case the effect was significantly less than that found in the seizure patients. Interestingly, the left-right differences in the nonseizure group were in the expected directions on all four tests, but these differences were far too small to attain significance. Given that seizure activity was the factor responsible for more frequent and more severe deficits, again no left-right differences would be expected, in this case presumably because the seizure activity, and/or seizure medication (*see below*), interfered with the functioning of both hemispheres.

The absence of laterality effects for IQ and memory measures in this young population of patients with hemispheric insult is broadly consistent with the hypotheses of hemispheric equipotentiality and cognitive crowding. The equipotentiality hypothesis (Lenneberg, 1967) refers to the ability of either cerebral hemisphere to subserve speech and language functions in the face of early unilateral damage. Support for this view is provided by earlier findings that neither left nor right hemisphere insult during early childhood results in persistent speech or comprehension disorders, although initial injury to the left and sometimes the right cerebral hemisphere may cause transient dysphasia (McFie, 1961; Basser, 1962). To the extent that the nonseizure patients in the present study were unimpaired relative to the normal control subjects on measures of verbal IQ and verbal memory, the data could be accounted for by this hypothesis and, if so, would extend the domain of hemispheric equipotentiality beyond language *per se* to include verbal memory as well.

The cognitive crowding hypothesis (Teuber, 1975) states that although the remarkable plasticity of the immature brain enables the right cerebral hemisphere to mediate speech and language functions, at least at a gross level, after early injury to the left, the right hemisphere achieves this end at the cost of its own domain of specialization, namely visuo-perceptual and spatial functions. As a result, the predicted net effect of a unilateral cerebral insult suffered during early childhood, regardless of hemispheric side, is an impairment in various visuo-perceptual and spatial abilities. The performance of our nonseizure patients, who exhibited unimpaired language-related skills at the cost of a visuo-perceptual skill, is again consistent with this prediction.

Whereas lesions uncomplicated by seizures affected nonverbal functions almost exclusively, lesions accompanied by seizures adversely affected nearly all measures, nonverbal and verbal alike, including an exacerbation of the effects over and above the effects of the lesions alone on the nonverbal functions. The only exceptions to this conclusion were found in the subgroup where age at testing occurred after the age of 12 yrs. These older subjects with seizures failed to show greater impairment than those without seizures only on the immediate and delayed recall of the WMS logical memory subtest and on the paired associate-related words subtest. In the former case, the absence of a deficit is probably attributable to a floor effect, the scores of the NC and NS groups already being very low.

The deleterious effects of seizures as compared with brain damage alone is particularly evident in the comparisons between the subgroup with seizures and mild neuroradiological abnormality (n = 4) versus the subgroup without seizures and severe neuroradiological abnormality (n = 8). In these comparisons, the former subgroup was significantly impaired relative to the latter subgroup on verbal IQ, paired associate learning (unrelated words) and paired associated learning (third trial) (*see* Table 4). In no case did the nonseizure subgroup with severe abnormality show a greater impairment than the seizure subgroup with mild abnormality. This suggests that the critical variable underlying the deficits is not structural abnormality *per se*, but ongoing seizures. The present findings and their interpretation are consistent with those reported for measures of IQ (Süssová *et al.*, 1990).

Both of the above sets of findings lead to a conclusion opposite to that proposed recently by Levine *et al.* (1987), who have suggested that impairments on psychological measures in cases of childhood epilepsy are related to size of lesions rather than presence of seizures. One possible resolution of this apparent contradiction is provided by our finding that, in the cases without seizures, the subgroup with severe neuroradiological abnormality (n = 8) had a significantly lower performance IQ than the subgroup with mild abnormality (n = 19). Our combined results thus raise the possibility that, in childhood, large lateralized lesions of either hemisphere, provided they are unaccompanied by seizures, lower performance IQ selectively, whereas severe seizure activity, even in cases with small lesions, selectively lowers verbal IQ and verbal memory. Because the statistical comparisons on which it is based involve relatively small numbers of subjects, this suggestion must be considered speculative for now, but it can serve as a testable hypothesis for further study.

The presence of seizures was more deleterious than the presence of electrophysiological abnormality, suggesting that the pathology underlying seizure activity, even if the seizure activity was controlled as it was in some cases, was more disruptive than the pathology underlying nonseizure EEG abnormality. This conclusion must be qualified in an important way. It is possible that the anticonvulsant drug therapy administered to all of the seizure patients rather than the seizures, *per se*, may have been responsible for their impairments. There is an extensive literature on the adverse effects of medication therapy on the development of cognitive abilities (Thompson and Trimble, 1982; Corbett *et al.*, 1985; Rodin *et al.*, 1986), but there is a dearth of information on the specific contributions to psychological impairments of anticonvulsant agents versus seizures in children with hemiplegic cerebral palsy. An important issue for future investigation will be the attempt to disentangle the effects of these variables.

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APPENDIX

ABSENCE OF EFFECTS OF HEMISPHERIC SIDE OF LESION

	LNS		*RNS*		*LS*		*RS*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Verbal IQ	101.32	16.06	103.42	16.50	86.21	13.45	90.13	14.02
Performance IQ	98.64	14.02	97.92	15.25	83.86	12.72	90.25	12.36
Logical memory immediate recall	42.34	15.62	52.16	14.51	38.41	17.91	38.96	16.41
Logical memory delayed recall	32.99	17.33	41.77	15.24	29.75	17.07	29.24	19.04
Paired associate learning—related pairs	16.12	2.54	16.63	1.47	14.57	2.56	14.56	2.53
Paired associate learning—unrelated pairs	7.36	2.97	8.00	2.59	5.29	2.52	5.00	2.99
Visual reproduction immediate recall	8.36	2.75	8.10	2.49	7.14	2.82	7.16	2.53
Visual reproduction delayed recall	6.24	3.35	4.85	2.69	3.11	2.30	4.22	2.52
Paired associate learning third trial	8.93	1.61	9.33	1.05	8.21	1.25	7.75	1.77
Paired associate learning—delayed recall	8.75	1.84	9.46	0.72	7.64	1.45	7.44	1.79

ANNOUNCEMENTS

Courses

The following two courses are being organized by the Institute of Psychiatry (University of London), the Mandsley Hospital and Bethlem Royal Hospital.

'The Brain Damaged Patient—Recent Advances in Pathogenesis and Treatment', April 27–28, 1992

'Treatment and Care in Old Age Psychiatry', July 8–10, 1992.

For further information, contact Mrs Lee Wilding, Conference Office, Institute of Psychiatry, De Crespigny Park, London SE5 8AF (Tel: 071 703 5411, ext 3170, Fax 071 703 5896).

The Medical College of Wisconsin and Continuing Medical Education, Inc. announce the seventh in a series of courses. 'The Sharper Image in MRI' MR Angiography and Imaging of the Head, Spine and Musculoskeletal System, July 27–31, 1992, at the Broadmoor Resort in Colorado Springs, Colorado, USA. Fees: $495.00 before June 5, 1992, $545 00 after June 5, 1992. Contact: Marti Carter, CME, Inc., 11011 W North Avenue, Milwaukee, WI 53226, USA (Tel: 414 771-9520).

Conferences organized by The New York Academy of Sciences

'Myasthenia Gravis and Related Disorders: Experimental and Clinical Aspects' at Hyatt Regency Washington on Capitol Hill, Washington DC, USA, April 12–15, 1992

'The Neurohypophysis: a Window on Brain Function' at Dartmouth College, Hanover, New Hampshire, USA, July 16–20, 1992.

'The Melanotropic Peptides' at Palais des Congrès, Place de la Cathédrale, Rouen, France, September 6–9, 1992.

'The Role of Insulin-like Growth Factors in the Nervous System' at Crystal Gateway Marriott, Arlington, Virginia, USA, November 4–7, 1992.

For further information contact the Conference Department, The New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021, USA (Tel: 212 838-0230; Fax: 212 888-2894).

The Fourth Annual Symposium—Treatment of Headaches and Facial Pain

This symposium will be held at the New York Marriot—East Side in New York City, April 26, 1992 For information contact Alexander Mauskop. The Downstate Headache Center, 132 Atlantic Avenue, Brooklyn Heights, NY 11201, USA (Tel· 718 935-9666).

The Ninth International Congress of Electromyography and Clinical Neurophysiology

This congress will be held in Jerusalem, Israel, June 8–12, 1992. For information contact Dr Arieh N. Gilai, Convener, EMG-CN-IX Congress, PO Box 29334, Tel Aviv 61292, Israel (Tel: 972 3 5102542; Fax: 972 3 660604).

The Second International Congress of Movement Disorders

This congress, jointly sponsored by the International Medical Society of Motor Disturbances and the Movement Disorder Society, will be held in Munich, Germany, June 24–26, 1992. For information contact Secretariat, ISMD, PO Box, CH-4005 Basel, Switzerland (Tel: +61 691 51 11, Fax: +61 691 81 89).

The Eleventh Annual Scientific Meeting and Exhibition of the Society of Magnetic Resonance in Medicine

This meeting will be held in Berlin, Germany, August 8–14, 1992. For further information contact SMRM, 1918 University Avenue, Suite 3C, Berkeley, CA 94704, USA (Tel: 510 841-1899; Fax· 510 841-2340)

Ultrasound Angiography 92—2nd International Conference

This conference will be held in the Medical and Biological Sciences Building, University of Southampton, UK, September 2–4, 1992. For further information contact Conference Secretariat, Ultrasound Angiography 92, PO Box 15, Eastleigh, Hampshire SO5 5XG, UK

The Second International Congress on Objective Assessment in Rehabilitation Medicine—Low Back Pain and Brain Injury

This congress will be held in Montréal, Québec, Canada, October 5–6, 1992. For further information contact Centre de formation en réadaptation du Québec, 6300 Avenue Darlington, Montréal, Québec, Canada H3S 2J4 (Tel: 514 340-2089; Fax: 514 340-2149)

AAEM 1992 Annual Meeting

The Thirty-Ninth Annual Scientific Meeting and the Fifteenth Annual CME Courses of the American Association of Electrodiagnostic Medicine (AAEM) will be held in Charleston, South Carolina, USA, October 14–18, 1992. For information contact The AAEM Office, 21 Second Street SW, Suite 306, Rochester, MN 55902, USA (Tel. 507 288-0100, Fax: 507 288-1225).

The Eighth Conference of the South East European Society for Neurology and Psychiatry

This conference will take place in Jerusalem, Israel, February 28–March 3, 1993. For information contact Professor S. Feldman, The VIII Conference of the South East European Society for Neurology and Psychiatry, c/o PO Box 50006, Tel Aviv 61500, Israel (Tel· 972 3 5174571; Fax: 972 3 655674).

Second International Conference on Stroke

This conference will take place in Geneva, Switzerland, May 12–15, 1993. For information contact N M. Bornstein, MD, International Conference on Stroke, c/o Kuoni Travel Ltd, 7 Rue de Berne, CH-1211, Geneva 1, Switzerland (Tel: 41 22 732 0888; Fax: 41 22 731 5078).

The Sixth Congress of the European College of Neuropsychopharmacology

This congress will take place in Budapest, Hungary, October 10–14, 1993. For information contact Peter Gaszner, Huvosvolgyi út 116, Budapest, H-1021, Hungary *or* Congress Bureau MOTESZ, Ms Krisztina Szigedi (Tel 361 251-7999, 163-0037, 163-3899, Fax: 361 183-7918).

Peter Debye Prize 1992 on 'Aging of the Brain'

The University of Limburg at Maastricht, The Netherlands, has been given the opportunity of awarding a scientific award, the Peter Debye Prize, once every two or three years. The Peter Debye Prize 1992 on 'Aging of the Brain' has been awarded to Dr John Hardy from the Department of Biochemistry, St Mary's Hospital Medical School, London, UK, in recognition of his achievements in uncovering a cause for Alzheimer's disease, the most common disease which afflicts the aging brain. The prize was presented on January 10, 1992, at the Academic Ceremony on the occasion of the 16th Dies Natalis of the University.

Foundation Fyssen 1992/1993 Fellowships and the 1992 International Prize

The deadline for applications for the fellowships is March 31, 1992, and the effective date is October 1, 1992 (same topics and same dates each year), The deadline for nominations to the prize is September 1, 1992. Subject considered. elementary mechanisms of cognitive development. For information contact Colette Leconte, Executive Secretary, Foundation Fyssen, 194 rue de Rivoli, 75001 Paris, France (Tel 33 (1) 42 97 53 16; Fax· 33 (1) 42 60 17 95)

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REVIEW ARTICLE

NEUROLOGY OF OTOLITH FUNCTION

PERIPHERAL AND CENTRAL DISORDERS

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SUMMARY

The otolith organs detect gravitoinertial forces acting on the head providing signals to the brain which are essential for spatial orientation, sensing motion and organizing motor behaviour. Although the pathophysiology of otolithic dysfunction is poorly understood, a disorder of otolith function, at a peripheral or central level, may be suspected when a patient describes symptoms of false sensations of linear motion or tilt or shows signs of specific derangements of ocular motor and postural, orienting and balancing responses. When disorientation is severe the patient may describe symptoms which sound bizarre, raising doubts over the organic basis of the disease. Our recognition of an otolithic disorder and understanding otolithic involvement in a wider neurological context may be guided by knowledge of otolith physiology and of the characteristics of the few proven otolithic syndromes.

INTRODUCTION

A significant number of patients presenting to neurologists have symptoms of dizziness or disorientation, impairment of eye movement, balance or gait which are suggestive of disorders of otolith function and yet diseases of the otoliths are poorly represented in our diagnostic repertoire. As a consequence, the signs and symptoms of these patients are frequently misunderstood and they often remain without firm diagnosis. The foundations of an adequate nosology of otolithic disease depends upon knowledge of normal and disordered otolithic function and the ability to specify the nature and site of pathology. We are lacking in both these respects. Investigation of the otoliths is difficult because of the intricate interplay between otolithic signals and other sensory-motor functions. Furthermore, existing imaging techniques and probes are not able to demonstrate small lesions of the inner ear and brainstem pathways which are the primary structures for otolith function. As a consequence, our recognition of otolithic disease is based upon the clinical features of the few cases in which otolithic pathology has been identified and on what is known about the normal otolith functions. In this article, evidence will be presented for the importance of otolith involvement in peripheral labyrinthine and brainstem disease.

Normal physiology of the otoliths: symptoms

The sensory receptors of the otolith organs are the maculae which consists of a flattish

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membrane of innervated epithelium which projects hair cells into the overlying otolith membrane which, in turn, is overlain by a dense layer of calcium carbonate crystals, the otoconia. The utricular macula lies in the utriculus with its surface oriented approximately to the plane of the horizontal semicircular canals, which is tilted rostrally upwards by about 30°. The macula of the sacculus is oriented approximately at right angles to the utriculus lying in the sagittal plane. Within each macula the sensory hair cells are morphologically oriented in opposite directions on either side of, and at right angles to, a central line of demarcation named the striola. The striolae follow curved paths across the planes of the maculae so that there are hair cells oriented to respond effectively in all directions in the plane of the macula (Fig. 1).

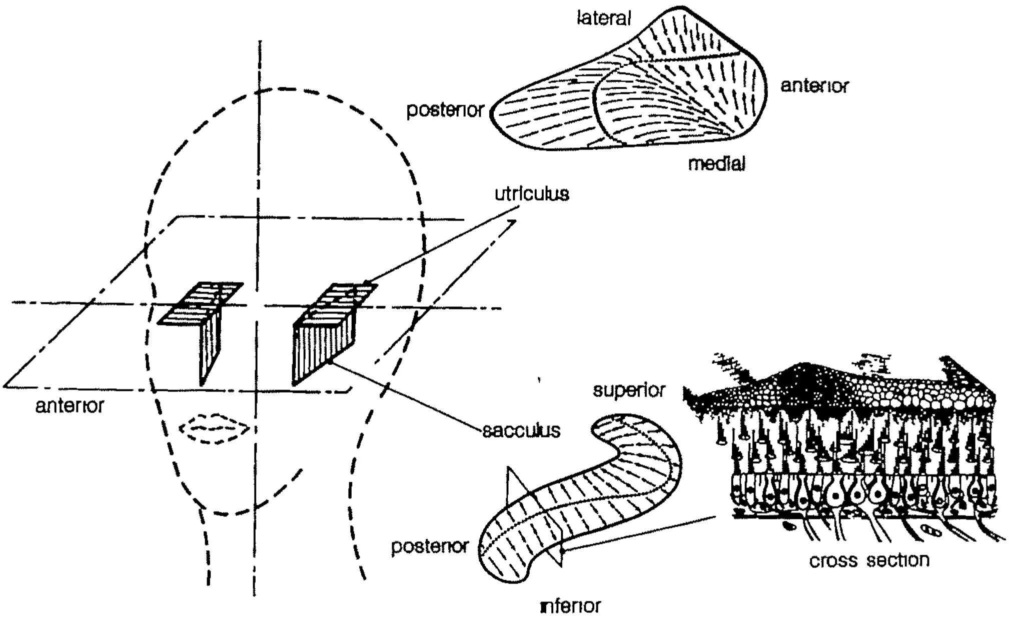

FIG. 1. Anatomical localization and structural organization of the otolith organs [redrawn from Spoendlin (1966) and Barnes (1980)]. The dotted line across the planes of the maculae of the utriculus and sacculus represents the striola which also corresponds approximately to the peak in the shape of the otoconial layer as shown in the cross-section. The arrows indicate the orientational direction of the hair cells with the arrow heads being the large kinocilium and the tail representing the smaller sterocilia; shown in the cross-section as resembling 'organ pipes' The afferent nerves support a resting discharge. Deflection of the hairs in the direction of the kinocilium is excitatory leading to an increase in frequency of impulses in the afferent nerve. Deflection away from the kinocilium causes a reduction in the discharge frequency in the afferent nerve

The stimulus to the hair cell receptors is gravitoinertial force. By Newton's first law a force acting on a body tends to accelerate that body and its inertia resists the action of the force. Thus, if the head accelerates linearly in the plane of a macula the hair cells tend to deflect in the opposite direction to the motion under the inertial load of the overlying otoconia; much like people standing on a train which suddenly begins to move, sway opposite to the motion. Less obvious is the equivalence between gravity and acceleration. Gravity is felt as a force acting downwards and is an acceleration in the upwards direction such that if the plane of the macula is oriented vertically the otoconia hang dependent causing hair cell deflection (the same stimulus would arise if the macula were oriented horizontally and subjected to a constant acceleration). The orthogonal planes of the utriculus and sacculus, each having multidirectionally oriented hair cell receptors, are structured to provide an effective signal for all directions of movement or tilt with respect to gravity (Fig. 1).

Recordings from the primary otolithic afferents in the vestibular nerve have shown signals relating acceleration and rate of change of acceleration (Fernández and Goldberg, 1976*a*,*b*,*c*) from which may be deduced that the otoliths have dynamic functions related to transient motions of the head and changes in orientation with respect to gravity and static functions related to posture with respect to the gravity vector. The major established pathways in the central nervous system (CNS) subserving otolith functions are shown in Fig. 2.

Symptoms of otolith dysfunction

There is physiological evidence that otolithic signals have important roles in the sense of uprightness and postural control and in the perception of organization of responses to linear motion, of which an important aspect is eye and head movements, especially in the vertical pitch ('yes-yes' direction) and roll (head tilt ear down to shoulder) planes. In subserving these functions otolith signals converge and interact with other sensory modalities and motor mechanisms so that otolith dysfunction may occur with lesions of peripheral and central pathways in the nervous system.

If patients' symptoms and signs reflect normal otolith functions we may assume that disorders involve multisensory illusions of linear motion and tilt, postural imbalance and gait ataxia and abnormal eye movements. Accordingly, we suspect otolithic disease when patients report: false feelings that themselves or the ground is moving, either vertically as walking on a mattress or tilting as on the deck of a ship; sudden veering (lateropulsion) or feelings of falling. Of importance, the illusory sensations are not necessarily confined to a feeling inside the head but are referred to a perception about motion of the whole body as if the patient were standing on a moving surface. Visual symptoms suggestive of otolithic disease may include diplopia, particularly in vertical and oblique directions due to misalignment of the eyes with the horizontal plane; oscillopsia due to paroxysmal involuntary eye movements and to abnormal compensatory vestibular reflexes, particularly for vertical head motion; inability to align objects such as a picture on a wall to the vertical.

In some syndromes patient's symptoms would lead one to suspect that the underlying disorder is predominantly otolithic in nature and fortunately, for some of these syndromes, there is evidence for primary otolith disease. We next describe the most important of these syndromes together with the evidence, hard or speculative, for their otolithic nature. A more comprehensive classification is given in Table 1 where syndromes are grouped under symptoms as a guide to differential diagnosis. Important features for diagnosis are whether symptoms are paroxysmal or sustained, whether they are spontaneous when the head is upright or provoked by tilt or head motion. One should also be aware that clinical signs suggestive of disordered otolith function may frequently be *asymptomatic*. For example, positional nystagmus is a nystagmus which is provoked

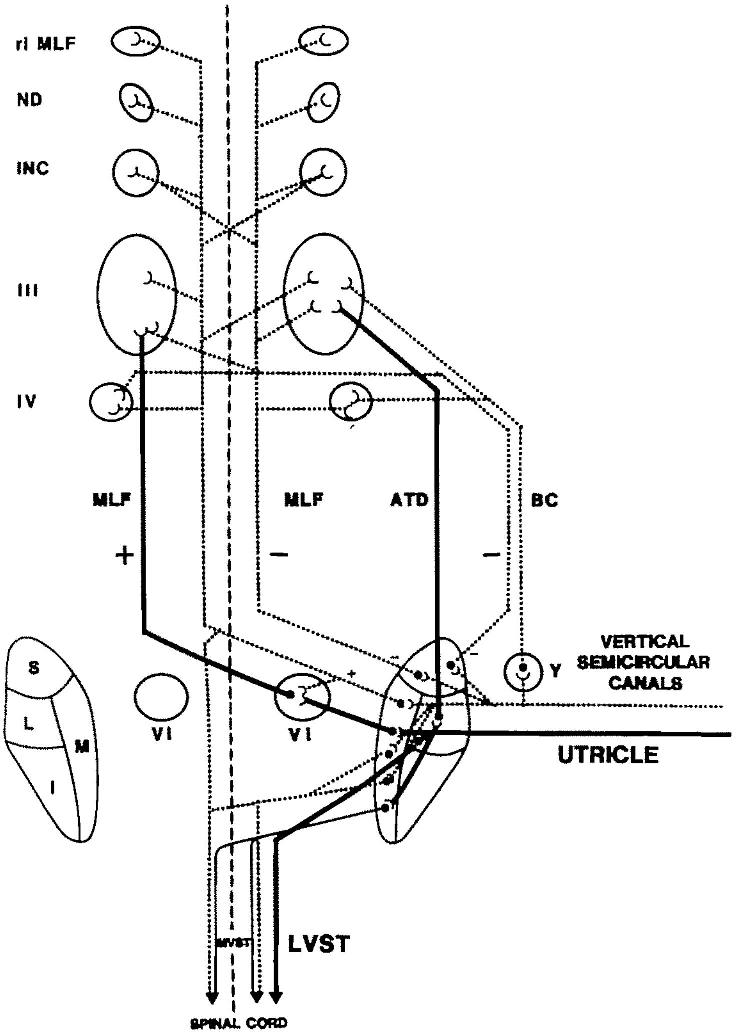

FIG. 2. Projections from utricle and vertical semicircular canals to oculomotor nuclei (trochlearis IV, oculomotorius III) and supranuclear centres of nucleus interstitialis of Cajal (INC), nucleus of Darkschewitsch (ND) and the rostral interstitial nucleus of the fasciculus longitudinalis medialis (ri MLF) (after animal studies by Tarlov, 1970; Gacek, 1982; Graf and Ezure, 1986). Projections from the utricle (bold line) mainly travel from the lateral vestibular nucleus (L) via the ipsilateral ascending tract of Deiters (ATD) to the ipsilateral oculomotor nucleus (medial rectus muscle) and via the medial vestibular nucleus (M) and the contralateral MLF to the contralateral oculomotor nucleus. Excitatory projections from the vertical semicircular canals travel from the rostral part of the medial vestibular nucleus (+) via the contralateral MLF to the oculomotor nuclei and supranuclear centre in the mesencephalic tegmentum. This pathway corresponds with the pathway of the utricular projections within the contralateral MLF. Convergence between otolith and canal input is most probable An inhibitory projection from the vertical semicircular canals connects the superior vestibular nucleus (S) and the ipsilateral oculomotor nuclei via the ipsilateral MLF. There is another inhibitory pathway connecting the superior vestibular nucleus with the contralateral trochlear and oculomotor nuclei via the ipsilateral brachium conjunctivum (BC). There are some neurons with input from the saccule and the vertical canals, which travel via the Y-nuclei (ncl infracerebellaris) and the ipsilateral brachium conjunctivum towards the more rostral oculomotor nuclei. MVST and LVST represent the medial and lateral vestibulospinal tracts for postural control. Thus, otolithic and canal input is conveyed by pathways, which closely travel together and (probably) converge within the contralateral MLF. I = inferior vestibular nucleus.

TABLE 1. SYNDROMES PRIMARILY AFFECTING OTOLITH FUNCTION

Main presenting symptoms	*Other symptoms*	*History/ aetiology*	*Signs*	*Hypothetical mechanism*
		Post-traumatic otolith vertigo		
Head motion intolerance. Inducing a to-and-fro vertigo and oscillopsia with gait ataxia, 'noncerebellar' type		Head or whiplash injury Spontaneous degeneration in the elderly	Perceived visual deviation of subjective vertical (head tilt, body lateropulsion, skew deviation cyclorotation?)	Dislodged otoconia cause unequal heavy loads with otolith tone imbalance
Refs.: Brandt and Daroff, 1980, Brandt, 1991*a*.				
		Perilymph fistual of otolith type		
	To-and-fro vertigo and oscillopsia with sneezing, coughing and physical exercise	Barotrauma, physical exercise, otosurgery	Positive fistula signs (e.g Valsalva monoeuvre)	Perilymph leakage/ abnormal elasticity of bony labyrinth with irritative otolith stimulation during head motion/intracranial pressure changes
Refs.: Healy *et al* , 1974; Deecke *et al.*, 1981.				
		Vestibular atelectasis		
		Occurs with inner ear disorder or idiopathic vestibular loss uni- or bilateral		Collapse of the walls of the ampulla and utricle
Ref : Merchant and Schuknecht, 1988.				
		Endolymphatic hydrops (e.g. Meniere's disease)		
	Episodic vertigo, tinnitus, fullness of the ear	Inner ear disorder or idiopathic	Hearing loss	Deformation or pressure changes in the membraneous labyrinth
Ref.: Schuknecht, 1984.				
Differential diagnosis· otosclerosis, labyrinthitis, autoimmune inner ear disease, temporal bone fracture/haemorrhage				
		Vestibular drop attacks—Tumarkin's otolithic crisis		
Sudden falls	Episodic vertigo, tinnitus, fullness of the ear	Inner ear disorder, idiopathic Meniere's disease (early or late stage)	Hearing loss, vestibular dysfunction	Sudden changes in endolymphatic fluid pressure with inappropriate otolith stimulation causing reflex-like vestibulo-spinal loss of postural tone
Refs.: Tumarkin, 1936; Black *et al* , 1982; Baloh *et al.*, 1990				
Differential diagnosis: Cardiac, cerebrovascular and psychogenic drop attacks as well as seizures; in majority aetiology remains unknown.				

TABLE 1 (*continued*)

Main presenting symptoms	*Other symptoms*	*History/ aetiology*	*Signs*	*Hypothetical mechanism*
Benign paroxysmal positioning vertigo (BPPV)				
Positioning rotational vertigo. Initially combined with motion intolerance and gait ataxia, nausea, vomiting		Head or whiplash trauma days or weeks before earlier episodes of same vertigo. Idiopathic	Torsional positioning nystagmus with latency and fatigue	Overexcitability of the cupula of the posterior canal due to the heavy load (cupulolithiasis); rarely affects the anterior or horizontal canal, may be bilateral, there may be an exaggerated post-rotatory response
Refs. Schuknecht and Ruby, 1973, Epley, 1980.				
Differential diagnosis: Neurovascular cross compression, central vestibular nystagmus and vertigo with lesions of the vestibular nuclei, perilymph fistula, Meniere's disease, drug or alcohol intoxication.				
Peripheral ocular tilt reaction				
Sustained lateral head tilt. Perceived tilt of visual scene, vertical or oblique double vision, postural imbalance and falls		Barotrauma, physical exercise, post otosurgery, inner ear disease	Skew deviation cycloration, deviation of visual vertical towards head tilt	Otolith (utricular) tone imbalance due to unilateral loss or irritation of the utricle or nerve
Ref.: Halmagyi *et al.*, 1979.				
Central ocular tilt reaction				
		Brainstem disorders (infarction, haemorrhage, multiple sclerosis, head injury)	Skew deviation, cyclorotation, deviation of visual vertical plus other brainstem signs	Irritation or lesion of central graviceptive pathways
Refs : Brandt and Dieterich, 1987; Halmagyi *et al.*, 1990; Dieterich and Brandt, 1992.				
Differential diagnosis: Head tilt secondary to vertebral/muscular disorders, peripheral ocular motor palsy, spasmodic torticollis, habitual attitudes				
Otolith Tullio phenomenon				
Paroxysms of lateral head tilt. Induced by sound stimulation		Barotrauma, exercise post-otosurgery, inner ear disease	Skew deviation cyclorotation, postural imbalance induced by loud sounds	Inappropriate mechanical stimulation of (utricular) otolith (e.g. subluxation of stapes footplate)
Refs.: Deecke *et al.*, 1981; Vogel *et al.*, 1986; Dieterich *et al.*, 1989.				

TABLE 1 (continued)

Main presenting symptoms	*Other symptoms*	*History/ aetiology*	*Signs*	*Hypothetical mechanism*
		Paroxysmal central ocular tilt reaction		
Spontaneous or by changing head position		Brainstem disorder (e g. abscess, MS)	Proxysms of skew deviation cyclorotation, deviation of visual vertical and other brainstem signs	Excitation of graviceptive pathways by ephaptic spreading in ipsilateral lower or contralateral rostral brainstem lesions
Refs · Rabinovitch *et al.*, 1977, Hedges and Hoyt, 1982.				
		Otolithic paroxysmia		
Paroxysmal oscillopsia and to-and-fro vertigo	Diplopia (vertical/oblique), paroxysmal postural imbalance, rotatory vertigo, tinnitus		Paroxysmal skew deviation, cyclorotation with small amplitudes and with/without head tilt, hearing loss, vestibular hypofunction	Neurovascular cross compression at root entry of eighth nerve with ephaptic spreading
Refs.: Møller and Møller, 1990; Brandt, 1991*a*				
		Upbeat and downbeat nystagmus		
Central positional nystagmus Nystagmus provoked or modified by position	Sometimes with vertigo	Diseases of cerebellum and brainstem Arnold Chiari. Idiopathic		Disinhibited gravity effects on cerebellum and otoliths and abnormal interactions of canal and otolith signals in the cerebellum and brainstem
Ref.. Fisher *et al.*, 1983				

or significantly modified when a patient's head is placed in static tilts with respect to upright. In cases of peripheral vestibular disease the more typical forms of such nystagmus are transient and accompanied by vertigo. However, when positional nystagmus occurs in disease of the CNS the more typical forms are sustained as long as the patient is tilted and not accompanied by marked feelings of dizziness. As a rule of thumb, the presence of vestibular signs without accompanying vertigo is evidence in favour of a CNS disorder.

PERIPHERAL DISORDERS OF OTOLITH FUNCTION

Post-traumatic otolith vertigo

The frequency of dizziness and disequilibrium following head trauma may be as low as 14% for nonhospitalized patients (Coonley-Hoganson *et al.*, 1984) but in most studies incidence lies somewhere around 40–60% (Friedman *et al.*, 1945; Gannon *et al.*, 1978).

The origins of dizziness and disorientation following head injury are multiple, including concussion, particularly to the brainstem, trauma to the labyrinth and injury to the neck. Accordingly, identification of the specific causes of dizziness can be uncertain in many cases. However, some patients describe their post-traumatic vertigo as a nonrotatory to and fro illusion of motion which is particularly associated with head movement and an unsteadiness of gait similar to walking on a pliant surface. Since these symptoms suggest a disorder of sensation of linear motion one might suspect that the primary disorder is traumatic injury to the otolith organ (Brandt and Daroff, 1980). This hypothesis is corroborated by studies in animals demonstrating that high linear acceleration applied to the skull dislodge otoconia (Hasegawa, 1931; Igarashi and Nagaba, 1968). Thus it is envisaged that, with head injury in humans, calcareous material embedded in the gelatinous matrix may be loosened by impact, resulting in unequal loads on the macula beds and a tonus imbalance between the two otolith organs. De Wit and Bles (1975) found that postural sway is increased after head shaking, in dizzy patients who have suffered a concussion and that they are more dependent upon visual stabilization than normal subjects suggesting that their labyrinthine function is unreliable. Although the authors believed these findings resulted from brainstem concussion, there is the alternative, or additional explanation that the head shaking could further dislodge precariously seated otoconia causing an acute otolithic imbalance.

Up to now there has been no clinical test available to establish the diagnosis of post-traumatic otolith vertigo. However, we have unpublished evidence for a transient deviation of the subjective visual vertical in these patients and a similar deviation is found in patients with benign paroxysmal vertigo which is known to arise from cupulo lithiasis (Schuknecht, 1969; Schuknecht and Ruby, 1973).

In cases of purely peripheral vestibular lesions, central compensation promotes a gradual recovery from the vestibular imbalance which often takes place within days or weeks. In these cases exercise is the best therapy for expediting compensation (Brandt, 1991). With more severe head injuries in which there may be multifocal micro-vascular lesions in the CNS impeding compensatory mechanisms, the time course of recovery from a labyrinthine lesion may be prolonged (Rudge and Chambers, 1982).

Benign paroxysmal positional vertigo

This form of positional vertigo is provoked characteristically by movements which take the head out of an upright position and so patients typically complain that the vertigo is triggered by reaching upwards or downwards or turning over in bed. It is also associated with head injury but also has idiopathic, vascular, degenerative aetiologies or may follow surgery (Dix and Harrison, 1984). In the clinic a provocative manoeuvre is the positioning test in which the patient is brought swiftly from sitting upright down to a supinated position with the head rotated to left or right with the ear down and neck extended and head dependent over the edge of the examination couch (Dix and Hallpike, 1952). The manoeuvre provokes a transient paroxysm of nystagmus accompanied by vertigo with a latency which may vary from a few seconds to more than a minute, so that there is a danger that some cases may be missed during examination. The response has a duration of a few seconds to a minute or so and is fatigued by repeated positioning. After an episode the patient may feel unwell for several hours to several days.

The nystagmus provoked is usually predominately torsional with a horizontal component beating to the undermost ear. In some patients we have observed that there may be a torsional nystagmus in one eye with a vertical nystagmus in the other with the appearance that the eyes are rotating about an axis passing through the labyrinth.

Benign paroxysmal positional vertigo has been attributed to detachment of otoconia from the otoconial layer and subsequent deposition, by head tilting, on the ampulla of the semicircular canals, thus altering their dynamics ('cupulolithiasis') (Schuknecht and Ruby, 1983; Epley, 1980). In the majority of unilateral cases the lesion is localized to the side of the undermost ear in the provocative tilting manoeuvre (Citron and Hallpike, 1956, 1962), but in many patients tilt to both right and left sides can be provocative. The recommended therapy for cupulolithiasis is head exercises which disperse the otoconial debris (Brandt and Daroff, 1980) and assist in the process of central compensation for imbalance caused by the altered otoconial mass of the damaged otolith organ (Rudge, 1983). It is also claimed that the vertigo may be relieved by posterior ampullary nerve section (Gacek, 1978). However, most cases resolve spontaneously over a period of several weeks or months. The presence of positional nystagmus which does not conform to this typical picture raises the possibility of CNS disease warranting further investigation.

Otolith type of perilymph fistula

Healy *et al.* (1973, 1974) were the first to stress that this condition should be suspected in patients with severe gait disturbances and ataxia without evidence of central nervous disease, even in the absence of gross hearing defects. Patients with an otolithic type of fistula can be free from vertigo with head stationary but experience a distressing to and fro illusory movement of the body and surrounds when the head is moved. Sometimes the linear vertigo may be described as a tilt or slow falling and can be precipitated in the supine position, especially with the affected ear undermost. Particularly provocative manoeuvres involve predominately linear head acceleration such as rising from seated position or walking, when the patient may describe sensations as if walking on pillows. Unlike canal disease, nausea and vomiting are rare and, despite severe ataxia, there is no spontaneous nystagmus. It may also be striking that angular head movements, such as head shaking in yaw, which stimulate the semicircular canals are much better tolerated than linear motion. The gait is broad based and ataxic but clinical examination excludes cerebellar or spinal ataxia.

The disease is more often episodic than chronic. Episodes are sometimes induced by strenuous activities such as lifting heavy objects, jogging or valsalva manoeuvres provoking pressure increases such as coughing, sneezing and straining. The severity of the episodes varies and some patients are able to detect the beginning of an attack by an audible 'pop' or increasing fullness of the ear so that they can prevent the development of more severe symptoms merely by stopping the precipitating activity.

The positive identification of a fistula mechanism, even at surgery, can be difficult (Ludman, 1984). Evidence in favour of a fistula is afforded by a history of explosive or barotrauma or the provocation of vertigo by manoeuvres raising intracranial pressure. When signs of canal dysfunction are absent it is justified to call the syndrome 'otolith type of perilymph fistula', since the vertigo symptoms can be explained by abnormal otolith function caused by a leak of perilymphatic fluid from the labyrinth secondary to oval window fistulas. The symptoms most often associated with this otolithic vertigo are fluctuating fullness in the ear, tinnitus and sensorineural hearing loss.

Otolith Tullio phenomenon

The Tullio phenomenon consists of transient vertigo and eye movement which are induced by sound and abate when the sound ceases. The patients complain about distressing attacks of vertical, oblique and torsional oscillopsia (apparent tilt of the visual scene) together with head jerking and postural imbalance consisting of a fall towards the affected ear and backwards which is elicited by loud sounds, particularly when applied to the affected ear with a maximum effect at a certain frequency (usually around 500 Hz). Uttering vowels, nose blowing and rapid pressure changes during tympanometry can cause similar symptoms of varying severity. The cause of the Tullio phenomenon is thought to be an abnormal transmission of sound-induced mechanical vibration to the vestibular labyrinth.

Cases reported in the literature (Deecke *et al.*, 1981; Vogel *et al.*, 1986; Brandt *et al.*, 1988; Dieterich *et al.*, 1989) describe a kind of Tullio phenomenon which is primarily due to selective otolith stimulation. Evidence for this in the patient of Dieterich *et al.* (1989) was afforded by surgical exploration of the middle ear which revealed a subluxated stapes footplate in a hypertrophic stapedius muscle. Since the footplate lies adjacent to the wall of the utricle, the mechanism of the phenomenon was thought to be a wave of compression, excitatory to the utricle, which was generated by pathologically large amplitudes of movement of a hypermobile stapes footplate when the stapedial reflex was evoked.

The features of the otolith Tullio is the presence, during the paroxysm, of one or more of the following triad of components: (i) a contraversive head tilt (i.e. away from the side to which the sound stimulus is applied); (ii) a skew with relative hyperdeviation of the ipsilateral eye; (iii) contraversive ocular torsion ('ocular torsion' is rotation of the eye about the optical axis, this is sometimes termed 'counter-rolling' if in response to head tilt, and 'cyclorotation' in the context of strabismus). This pattern of synkinesis has been termed 'ocular tilt reaction' (OTR). An inverse pattern to the excitatory OTR is given by lesion of the utricle which induces an ipsiversive OTR, due to unopposed tone from the remaining intact utricle (Halmagyi *et al.*, 1979). The OTR is thought of as a fundamental pattern of coordinated eye-head motion in roll. In mammals with lateral eyes, the OTR is a normal response to head tilt and corrects eye and head posture to a more upright position (Magnus, 1924). In normal humans tilt in roll provokes head righting and ocular counter-rolling, although there is current debate as to whether there is any significant skewing of the eyes in human subjects.

The specific role of the utricle in generating the OTR is supported by experimental findings in guinea-pigs (Curthoys, 1987), using electrical stimulation of localized spots on the utricular macula, and in cats (Suzuki *et al.*, 1969), with stimulation of the utricular nerve. Stimulation evokes elevation of the ipsilateral eye together with contraversive torsion. This pattern is consistent with the synaptic organization of utricular inputs to spinal and oculomotor neurons from which one would expect head and body tilt and conjugate ocular torsion with disconjugate vertical divergence (Reisine and Highstein, 1979; Carpenter and Cowie, 1985). Physiological evidence for the otolithic origin of the OTR is summarized in Table 2.

TABLE 2 PHYSIOLOGICAL EVIDENCE OF OTOLITHIC CONTROL OF EYE AND HEAD MOVEMENTS

Stimulation	*Utricle*	*Saccule*	*Authors*
Eyes	Nerve plus macula Predominantly conjugate contraversive torsion of both eyes Disconjugate ipsilateral upward, contralateral downward shift.		Suzuki *et al.*, 1969 (cat)
	Small conjugate contralateral shift	Ipsilateral upward rotation	Kubo, 1906 (fish)
	Macula Ipsilateral upward or upward-torsional movements. Contralateral downward movement. No horizontal eye movements	Macula Same effects as with utricle stimulation	Curthoys, 1987 (guinea-pig)
	Macula Disconjugate rotatory and vertical components		Szentágothai, 1964 (dog)
		Inferior macula Ipsilateral clockwise rotation, contralateral depression	Fluur and Mellstrom, 1971 (cat)
	Macula Elevation of one eye while depression of the other. Ipsilateral elevation, contralateral depression		Maxwell, 1920/1921 (dogfish, ray) Ulrich, 1935 (pike)

Lesion	*Utricle*	*Saccule*	*Authors*
Eyes	Nerve Disconjugate, ipsilateral, downward, contralateral upward deviation. Without spontaneous nystagmus	Macula No changes in eye position	Versteegh, 1927 (rabbit)
Head/body	Nerve Ipsiversive head tilt	Nerve plus macula No changes in head position	Veersteegh, 1927 (rabbit)
	Ipsiversive lateropulsion with falls for 3 wks	No lateropulsion and falls only slight vestibulo-spinal imbalance	Igarashi *et al.*, 1972 (squirrel, monkey)

CENTRAL DISORDERS OF OTOLITH FUNCTION

The central disorders of otolith function into which we have some insight concern eye-head coordination, positional nystagmus and, to a lesser extent, vestibulo-spinal function. In each case one is dealing with static effects related to posture and gravity and dynamic effects in locomotion. As a rough division, abnormal static effects on eye movements result in skews and torsional displacements whereas dynamic disorders manifest as nystagmus and abnormal compensatory reflexes. Static effects on posture result in head and body tilts whereas incoordination, particularly gait ataxia, signifies disorder of dynamic otolith-spinal function.

Otolith dysfunction involving eye-head coordination in roll

Evidence from peripheral otolith dysfunction shows that the 'graviceptive' input from the otoliths plays an important role in stabilizing the posture of the eyes, head and torso in the normal upright position. As with peripheral disturbances, a unilateral lesion of otolithic pathways, anywhere from the periphery to the rostral brainstem tegmentum, causes an imbalance in vestibular tone which may result in disturbances of coordination in roll (i.e. movements in the coronal plane) including: (i) tilt of the internal representation of uprightness (subjective visual vertical); (ii) vertical divergence of the eyes (skew deviation); (iii) conjugate torsional deviation and head and body tilt (lateropulsion). The primary pathways subserving otolith ocular and otolith spinal control are illustrated in Fig. 2.

A partial or complete OTR may result from destructive or irritative lesions of central vestibular pathways. The OTR was first delineated by Westheimer and Blair (1975*a*,*b*) who provoked the coordinated sequence in primates by electrical stimulation of the rostral midbrain tegmentum in a region dorsolaterally to the third and fourth nuclei and extending rostrally to include the nucleus of Cajal. In human subjects, Sano *et al.* (1972) reported head extension (retroflexion) or ipsilateral head tilt induced by stereotaxic electrical stimulation of the interstitial nucleus of Cajal (INC) or adjacent areas of the medial longitudinal fasciculus. Stimulation of the INC in one patient with a history of post-traumatic see-saw nystagmus activated, or reproduced the nystagmus together with concurrent head tilt (together making a pattern of probable full OTR) which was abolished by electrocauterization of the area. Stimulation of the area adjacent and caudal to the INC resulted in head tilt solely. Thus until recently the midbrain tegmentum around the INC was thought to be the critical structure in the elicitation of OTR. A more recent study by Lueck *et al.* (1991) of a patient undergoing stereotaxis for thalamic pain, reported ipsilateral head tilt and skew with torsional nystagmus, whose slow phase was in the direction of the tilt, evoked by electrical stimulation in a region localized as the INC by stereotaxic coordinates. This is in agreement with magnetic resonance imaging (MRI) investigations of OTR associated with paramedian thalamic infarctions (Dieterich and Brandt, 1992) and points to the INC itself being the critical structure involved rather than the surrounding tegmentum.

There have been reports of few cases of paroxysmal OTR accompanied by oscillopsia in brainstem lesions. Rabinovitch *et al.* (1977) described a patient with multiple sclerosis who had paroxysmal OTR with paroxysms of vertical and horizontal pendular nystagmus. Hedges and Hoyt (1982) reported a paroxysmal OTR in a patient with a focal brainstem abscess which involved the rostral midbrain and the area of the subthalamus and zona incerta ipsilateral to the direction of the head tilt.

Tonic OTR is not a rare entity in brainstem disease occurring with both upper brainstem lesions and in Wallenberg's syndrome with lateral medullary lesions (Brandt and Dieterich, 1987; Dieterich and Brandt, 1992). The occurrence of OTR in Wallenberg's syndrome had hitherto escaped notice in the literature, although single components such as skew deviation, and diplopia with tilted images due to dissociated cyclodeviations of the eyes have been reported (Moberg *et al.*, 1962; Silfverskiöld, 1965; Hagström *et al.*, 1969; Hörnsten, 1974). In acute lateral medullary lesions, OTR is probably caused by interruption of ascending otolith and posterior canal input near the vestibular nuclei. There is clear evidence that a lesion of the lateral medulla causes an ipsiversive OTR, whereas unilateral mesodiencephalic lesions (paramedian thalamic infarctions), cause contraversive OTR (Halmagyi *et al.*, 1990). The opposed directions of OTRs, whether they are induced by rostral or caudally sited lesions in the brainstem, imply that the graviceptive pathways cross between the vestibular nuclei and the contralateral nucleus of Cajal. This crossing is probably in the upper pons as indicated by an analysis of more than 100 cases of brainstem vascular lesions (Brandt and Dieterich, 1992).

The way in which lesions in the lower and upper brainstem respectively induce OTRs is not yet understood and it is possible that there are different forms of the reaction. The ipsiversive OTR associated with lesions in the caudal brainstem in the environs of the vestibular nuclei is almost certainly due to combined lesions of pathways of the ascending otolith reflex to oculomotor neurons together with descending vestibular pathways to the neck (Halmagyi *et al.*, 1990). In contrast, although lesions in the rostral brainstem causing a contraversive OTR can be sited on vestibular ocularmotor pathways, they cannot affect direct vestibular-neck projections and an alternative mechanism must be sought for the cause of the head tilt. So it is possible that the rostral lesions involve descending, higher order mechanisms of head and eye coordination which are not solely vestibular.

Stimulation or lesions of the otoliths especially the utricle cause vertical divergence of the eyes (skew deviation) and cyclorotation of the eyes in the roll plane. Thus, skew deviation and cyclorotation in central vestibular pathway lesions most probably indicate otolith pathway lesions. Cyclorotation of the eyes and subjective visual vertical were measured in a total of 111 patients, most of them suffering from acute vascular brainstem lesions, in order to determine the differential effects of central vestibular pathway lesions on ocular motor and perceptual control in the roll plane (Dieterich and Brandt, 1992). The incidence of pathological findings was surprisingly high with 94% of the patients having deviations of subjective visual vertical. A further 88% of the patients exhibited pathological cyclorotation of one or both eyes irrespective of the level of the brainstem lesion. Vertical divergence of the eyes was observed in 31% and was most frequent in lateral medullary lesions (Wallenberg's syndrome). A complete OTR, which is assumed to represent otolith and/or vertical canal dysfunction was present in 20% of the patients (Brandt and Dieterich, 1987; Halmagyi *et al.*, 1990; Dieterich and Brandt, 1992). Most of the patients had additional cyclorotation of the eyes towards the side of the lesion. One-third of the patients who were presumed to have the most extensive vestibular lesions showed complete OTR in addition to body lateropulsion and a tendency to fall to the lesioned side.

Thus we hypothesize that deviation of the subjective visual vertical, lateropulsion of the body, skew deviation and cyclorotation of the eyes are the common perceptual, oculomotor and postural consequences of a unilateral lesion of otolith and vertical canal pathways producing an asymmetry of tonus in the roll plane. The postural asymmetries following vestibular lesions may have two intepretations. At the simplest level there is an interruption of direct reflex motor pathways causing tonic imbalance. At a higher level of organization, the asymmetries may be an adjustment of the body long axis to align with what the nervous system erroneously computes as being vertical (Brandt and Dieterich, 1987). The lesion induces a pattern of vestibular imbalance as if the eye and head were contraversively tilted; the ipsiversive OTR compensates for this apparent tilt (Fig. 3).

Positional nystagmus

Positional nystagmus is nystagmus which is elicited by tilting the subject from the upright position. Positionally sensitive nystagmus may be present when upright but is significantly modified by tilt. The effect of tilt on the nystagmus is thought to be mediated by the pattern of otolithic stimulation in the tilted attitude. There is a further distinction to be made between nystagmus provoked or modulated by the dynamic phase of 'positioning' a subject as with the Hallpike manoeuvre (head vigorously supinated and rotated to ear down) which stimulates canals and otoliths, and the 'positional' effects on nystagmus of maintaining a static position which are due to the gravitational stimulus to the otoliths. Positional nystagmus is classified according to the planes of the semicircular canals, i.e. anterior and posterior vertical canals transducing roll and pitch (head

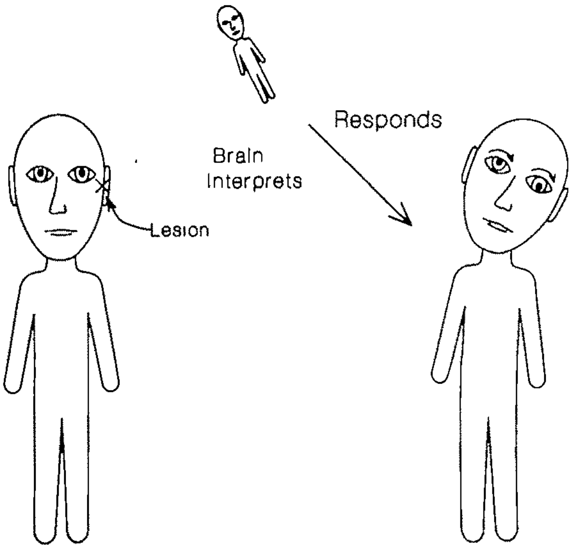

FIG. 3. Abnormal eye, head and body posture in lateralized vestibular lesions The torted eye posture and ipsiversive head and body tilt in unilateral peripheral or lateralized low brainstem vestibular lesions imitates the normal righting response to tilt. Skew in response to tilt is a feature of lateral eyed animals but it is an open question as to how much skew occurs in normal human subjects

motion in the coronal and sagittal planes) and yaw (motion in the transverse plane) since the nystagmus is probably related to otolith-canal interaction in control of compensatory eye movements (Barratt *et al.*, 1987; Gresty *et al.*, 1987; Brandt, 1991*b*).

Nystagmus in the coronal plane (roll)

In torsional nystagmus (TN) the eye rotates about the visual axis. Torsional nystagmus is frequently seen during Hallpike's positional manoeuvre in benign paroxysmal positional vertigo which, as described above, is of peripheral origin. Spontaneous TN however, in our experience, is due to CNS disease, particularly multiple sclerosis (MS), vascular lesions and posterior fossa tumours. Results from our own survey of 35 cases (Lopez *et al.*, 1992) showed that frequent findings were a caloric canal paresis on the side opposite that of the spontaneous TN and longer duration of horizontal caloric and rotational nystagmus in the same direction of TN. In agreement, MRI lesions were common in the area of the vestibular nuclear complex on the side opposite to the TN.

Although static positions of heat tilt influenced the TN, more frequent and consistent effects were obtained by vertical canal stimulation (head oscillation in roll). This was also the case for eight cases in whom an additional skew eye deviation was present. These results suggest therefore that TN originates in a central imbalance of vertical semicircular canal function resulting from lesions involving the vestibular nuclei on the opposite side of the TN. At first sight, therefore, it would seem difficult to reconcile these findings with the interpretation given above that skews, as part of an OTR, are otolithic in origin. It would be possible that TN and OTR are largely independent entities, the former depending on damage to vertical canal pathways and the latter to otolith pathways. The frequent coexistence of the two could be due to the close vicinity and convergence of otolith-canal pathways at various levels in the neuraxis. Further elucidation of this point will require selective vestibular stimuli in combination with precision eye-movement recordings.

Nystagmus in the lateral plane (yaw)

Positional nystagmus in the lateral plane may be *geotropic* in which the nystagmus beat is directed to the undermost ear or *apogeotropic* in which the beat is upwards. Since linear accelerations provoke compensatory otolith-ocular reflexes the tendency to respond to gravitational acceleration must be suppressed in normal circumstances. In apogeotropic nystagmus, which is the most common form of central positional nystagmus (Cawthorne *et al.*, 1969), the slow phase is in the opposite direction to (gravitational) acceleration as a compensatory response would be. Therefore apogeotropic nystagmus may be the release of compensatory eye movements as an inappropriate response because the brain has failed to ascribe the correct significance to the otolith signal and makes the interpretation of linear acceleration instead of gravitational acceleration. The rare geotropic positional nystagmus has a slow phase which is curiously in the same direction to the gravitational acceleration. During the dynamic phase of normal head tilt a lateral nystagmus is provoked which beats towards the direction in which the head is moving, resulting in a slow phase in the same direction as gravitational acceleration (Viéville and Masse, 1987). It may be that geotropic nystagmus is an inappropriate release of the lateral nystagmus usually seen during active tilt.

Although lateral positional nystagmus is a valuable sign of CNS disorder we are unaware of an adequate study in human subjects of the localization of the lesions responsible. Our own observations suggest that lateral positional nystagmus is associated with cerebellar disease (Gresty *et al.*, 1986*b*) and lesions of the brainstem in the environs of the vestibular nuclei, which is in accord with studies in primates demonstrating positional nystagmus with lesions of the nodulus and vestibular nuclei (Uemura and Cohen, 1973). The significance of geotropic vs apogeotropic positional nystagmus for functional localization has not been investigated.

Nystagmus in the sagittal plane (pitch)

A distinction may be made between nystagmus in the sagittal plane which is tilt sensitive and related to otolith function and nystagmus associated with vertical canal function (Gresty *et al.*, 1986*a*). In certain patients downbeat nystagmus appears only in specific head positions. Oscillation of the head about a position which does not provoke the nystagmus may give a normal vertical vestibular ocular reflex showing that the nystagmus is unrelated to canal function. In other cases the nystagmus is enhanced by head oscillation about all tilted positions suggesting that the nystagmus is related to asymmetry of vertical canal reflexes (Baloh and Spooner, 1981). Sometimes the nystagmus may be under canal and otolithic influences so that during tilt testing it is advisable to maintain the tilted position for several minutes until phasic canal-related effects decay and static otolithic influences are revealed.

Primary position upbeat nystagmus. The rare clinical entity of primary position upbeat nystagmus is almost always positional, being provoked by head tilt or, if present in head upright position, modified by tilt. The nystagmus is typically present in the primary position of gaze, beating upwards with respect to the head but may occur, paradoxically, on downgaze. It is often enhanced or provoked by vergence and frequently associated with lid nystagmus. Upbeat nystagmus should be distinguished from gaze paretic upwards beating nystagmus caused by an inability to maintain upwards gaze. Upbeat nystagmus is almost always central in origin and associated with lesions of the midline brainstem (Fisher *et al.*, 1983, Kato *et al.*, 1985; Hirose *et al.*, 1991), cerebellar vermis (Gilman *et al.*, 1977; Mehdorn *et al.*, 1979). A few patients have been reported with bilateral labyrinthine disease in whom upbeat nystagmus was present in the light (Gresty *et al.*, 1988). However, because there was no suppression of nystagmus in these patients and in spite of normal MRIs, the authors suspected additional subtle CNS disease for which there was no conclusive evidence.

Primary position downbeat nystagmus. Downbeat nystagmus is typically present in primary gaze beating downwards with respect to the head. It is often markedly enhanced with the eyes deviated laterally when it may beat in an oblique direction downwards and laterally and may also appear paradoxically on upgaze. Downbeat nystagmus should be distinguished from a gaze paretic nystagmus caused by an inability to maintain downgaze. Different series have shown that downbeat nystagmus is freqently secondary to Arnold Chiari malformation or to cerebellar degeneration (Cogan, 1968; Baloh and Spooner, 1981; Halmagyi *et al.*, 1938*b*; Bronstein *et al.*, 1987*a*). Many other causes have been described, including a fair proportion of idiopathic cases, vascular lesions of the brainstem-cerebellum, drug induced (particularly with lithium) MS and paraneoplastic. Although an otolith influence on the nystagmus can be frequently demonstrated by tilt, unfortunately tilt sensitivity lacks any localizing or aetiological value since tilt sensitive cases are present in all groups of patients (Bronstein *et al.*, 1987*a*).

Occasionally, in cerebellar degeneration, we have seen upbeating nystagmus reversing to downbeat nystagmus as a function of head position (Fig. 4). This is also reported in a patient with neuro-Bechet's disease in which the cerebellum was thought to be spared and the lesions responsible were probably in the brainstem (Ishikawa *et al.*, 1985). Upbeat nystagmus reversing to downbeat nystagmus on vergence has also been reported (Cox *et al.*, 1981). Reports of downbeat nystagmus with decompensated aqueductal stenosis, midbrain infarction (Slavin and Rosenberg, 1985) and of upbeat nystagmus changing over time to downbeating nystagmus in a patient with a thalamic arteriovenous malformation (Nowack and Clark, 1986), demonstrate that vertical nystagmus can also occur with more rostral lesions. The clinical features of downbeat nystagmus have been reviewed extensively by Schmidt (1991).

Vertigo and positional nystagmus. Vertigo rarely accompanies central positional nystagmus. However, one occasionally encounters patients with sustained positional vertigo which can be severely disabling (Watson *et al.*, 1981; Brandt, 1990). The precise localization of lesions responsible for central sustained positional vertigo is not established but typically the floor of the fourth ventricle is involved. On rare occasions a transient nystagmus, crescendo-decrescendo in magnitude has been observed in patients with CNS disorders, notably in tumours of the posterior fossa. The nystagmus may be multidirectional, possibly accompanied by objective vertigo and thus resembling benign positional vertigo (Watson *et al.*, 1981).

As a final note of caution, otolithic influence on eye movements demonstrates a curious lability. Several studies (e.g. Lichtenberg *et al.*, 1982; Israël and Berthoz, 1989) have reported that linear motions may provoke a nystagmus of arbitrary direction, even in normal subjects. This observation underlines the difficulties of interpreting nystagmus in patients who may have undergone extensive balance tests.

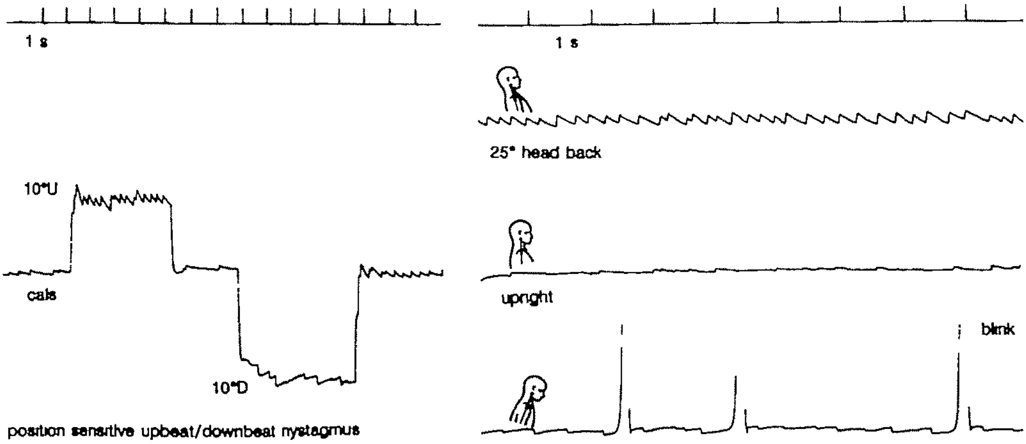

FIG. 4 Tilt sensitive upbeat-reversing to downbeat nystagmus in a male adult patient with idiopathic cerebellar degeneration

Unsteadiness due to otolith dysfunction

It is well known that disordered vestibular function produces abnormal posture, gait ataxia and susceptibility to falls, although there have been few studies of movement induced by otolithic stimulation. These have been concerned with responses to free fall or the Tullio phenomenon.

During a fall the muscles receive increased innervation to protect against the impact of landing. At least two distinct peaks of electromyographic (EMG) activity can be distinguished (Greenwood and Hopkins, 1967*a*). The first EMG burst in gastrocnemius occurs at a stereotyped latency of 75 ms and is vestibular in origin since it is absent in alabyrinthine subjects. The second peak is timed just before contact and is under multiple sensory and cognitive controls. Evidence of the otolithic origin of the early response is that it can be elicited by purely linear acceleration with a threshold of 0.2 g (Greenwood and Hopkins, 1976*b*). It is intact in patients with selective disease of the semicircular canals in whom nystagmus responses to rotation are absent (Halmagyi and Gresty, 1983).

Responses to falls may be studied safely with the subject lying on a cushioned couch which pivots around the foot end. The head is lifted to just above horizontal and is released unexpectedly (Halmagyi and Gresty, 1983*a*). The pattern of muscle activation is predominately extensor for prone falls and flexor for supine falls and thus seems to protect the head from hitting the floor (Stell *et al.*, 1990). A feature of cushioned fall is that the response tends to adapt with repeated trials.

Pathways for vestibulo-spinal responses. The latencies of muscle activation in response to sudden fall (Stell *et al.*, 1990) are typically 45 ms for blink, 43 ms for sternomastoid and 75 ms for quadriceps. The latencies of neck and leg muscles imply a spinal conduction velocity of 20 m/s which is similar to the conduction velocity for responses to auditory startle (Wilkins *et al.*, 1986) and slow in comparison with 60 m/s conduction velocity of the cortico-spinal tract in response to direct cortical stimulation (Hess *et al.*, 1987). In contrast, the existence of a fast vestibulo-spinal pathway has been demonstrated; galvanic stimulation of the labyrinth evokes muscle responses in triceps and soleus at latencies of 30 ms and 50 ms, respectively, and direct mechanical stimulation of the labyrinth evokes activity in gastrocnemius at 50 ms latency (Fries *et al.*, 1988, Dieterich *et al.*, 1989, Britton *et al.*, 1990) which are consistent with the latencies expected from the diameter of fibres in vestibulo-spinal tracts and comparable with the conduction velocity of cortico-spinal fibres.

Abnormal responses to unexpected fall. The short-latency response to falling is intact in patients with total unilateral loss of both canal and otolith function. This precludes its value for lateralizing vestibular dysfunction (Stell *et al.*, 1990). In patients with superficial frontal or fronto-parietal cortical lesions affecting the motor cortex, the response fails to adapt in the limbs contralateral to the lesion. In contrast, with deep lesions of the cerebral hemispheres, responses in the contralateral limb may be abolished. These findings indicate that the response is under cortical control but that the primary pathway is not through the motor cortex (Bronstein *et al.*, 1985). Lesions of the spinal cord delay or abolish the response on the side of the paretic limb (Bronstein *et al.*, 1985). We have studied the latency of the initial response in the quadriceps in patients with demyelinating disease and found statistically significant delays in latency comparable with those in sensory-evoked potentials or in motor responses to magnetic cortical stimulation (Hess *et al.*, 1987).

DIFFERENTIAL DIAGNOSIS OF OTOLITH DYSFUNCTION

Symptoms

The symptoms which are a consequence of vestibular disorientation may seem bizarre or can even be so strange that patients may find difficulty in finding words to describe their symptoms. Since otolithic dysfunction may give few physical signs it is not surprising that a common differential diagnosis in many cases is between psychogenic functional disorders.

Torsion and skew of the eyes

It may seem surprising that diplopia can occasionally result from a vestibular lesion. In fact heterotropia may occur with lesions at the vestibular end organ and within the CNS as well as in efferent oculomotor pathways. There is a current vogue to interpret skew and conjugate torsion as signs of involvement of central otolithic pathways and, hence, primarily vestibular phenomena. However, supranuclear lesions producing skew and torsion may involve not only vestibular pathways but also nonvestibular mechanisms of head-eye postural coordination and, if in the midbrain, may easily encroach upon ocular motor nuclei and nerves so that primary motor deficits may complicate the picture. Due to the difficulties in unravelling the causes of skew and torsion, many cases diagnosed as supra nuclear skew deviation may be mild trochlear nerve pareses (Bixenman, 1981).

A skew of vestibular origin may also be confused with a long-standing paralytic strabismus (for example, inferior rectus palsy) because a paralytic strabismus becomes more comitant with time due to contracture of the unopposed muscle and secondary changes in yoked muscles (von Noorden, 1977). In both the vestibular skew and comitant strabismus the eyes move fairly conjugately and for the strabismus a direction in which there is clear limitation of movement may not be obvious. Here the key to differential diagnosis is that the acute phase of an oculomotor palsy characteristically produces an incomitant strabismus. In contrast, an acute vestibular lesion produces a deviation affecting both eyes (Curthoys *et al.*, 1991) without limitation of movement. There is the additional consideration that conjugate torsional deviation of the eyes, typical of an acute vestibular lesion, would be rare in lesions of the oculomotor nerves because a precise bilateral pattern of disorder would be required.

Head tilt

A tilted head may be an idiosyncratic attitude which may be identified from old photographs of the observations of relatives. Alternatively, tilts and turns may be secondary to nystagmus where the turn brings the eyes into a quiescent position or control diplopia consequent to paralytic strabismus. Accordingly eye movements and tropia should be examined in all orbital positions. Abnormal head postures compensating for nystagmus are most frequently encountered in congenital-type nystagmus and alternating nystagmus (sometimes periodic) which may be congenital or acquired.

In torticollis as a manifestation of primary or secondary dystonia, there is clinically evident hypertonicity in the involved muscles which can be shown by EMG to be an order of magnitude greater than that found in normal subjects or in patients with unilateral vestibular lesions Bronstein *et al.*, 1987*b*; Bronstein and Rudge, 1988). The involved muscles also become hypertrophic. The direction of dystonic torticollis when in a rare association with unilateral labrinthine lesions is not related to the side of the vestibular lesion and so the vestibular insult appears to be one of the many trigger factors of the dystonia (Bronstein *et al.*, 1987*b*).

There have been no studies on the EMG activity of neck muscles in head tilt in OTR to establish whether the tilt involves normal postural tone or involves unusually high activity in specific muscles. Central causes of OTR frequently involve high brainstem lesions and it is known that experimental lesions in these areas can induce head tilt with heightened EMG activity which may be related to clinical dystonia (Hassler and Hess, 1954; Fukushima *et al.*, 1985; Fukushima-Kudo *et al.*, 1987).

TESTS OF OTOLITH DYSFUNCTION

Here we concentrate only on tests of otolith function which have been applied in a clinical setting. Due to the difficulties of separating otolithic from other sensory functions the reader should be aware that the tests described below may not be specific to otolith disorder and interpretation of the results may depend upon clinical context. In particular, the presence of signs of disease affecting central pathways of the vestibular system such as derangements of pursuit and optokinetic responses, failure of VOR suppression, failure of fixation suppression of spontaneous nystagmus and the involvement of other systems will give clues as to whether the disorder is at a peripheral or central level.

Visual vertical

The most simple test which is sensitive to unilateral loss of otolith function is alignment of the visual vertical. Judgement of verticality is sensitive to context, such as the walls of the room, therefore subjects should orient a rod to vertical or horizontal with external cues to uprightness excluded. Normal subjects can orient the visual vertical with an accuracy of 1°, range ±2° (Friedmann, 1970). Patients with bilateral loss of labyrinthine function are also able to orient the visual vertical but generally with less accuracy (Mann, 1951; Miller and Graybiel, 1966), showing that proprioception plays some part in this talent. In patients with unilateral labyrinthectomy, Friedmann found variable results; some subjects were normal in orienting the visual vertical whereas others showed a pathological deviation of the vertical in the direction of tilt towards the operated side, which, in occasional patients, could last for years after surgery. In contrast, in patients studied 1 wk after labyrinthectomy, Curthoys *et al.* (1991) found a consistent deviation of the visual vertical towards the side of the lesion averaging 11.7°, which decreased with time but could last, in some patients, for months.

The visual vertical can also be a useful test for a dysfunction of orientation in CNS disorders. In lower brainstem lesions Friedmann (1970) and Dieterich and Brandt (1992) found that the vertical was deviated to the side of the lesion. Upper brainstem lesions cause contraversive deviations of the vertical whereas dorsolateral, thalamic and cortical lesions can cause either ipsiversive or contraversive deviations which tend to be of smaller amplitude (Dieterich and Brandt, 1992).

A complicating factor in estimating the visual vertical is ocular torsion, since verticality is related partly to retinal coordinates (Howard, 1982). In a recent study, Dieterich and Brandt (1992) have shown in patients with labyrinthine and brainstem disease with ocular torsion, that the deviation of the visual vertical is independent of, and often greater than, the amount of eye torsion as measured on fundoscopy. This important result allows one to differentiate between a vestibular and visual contribution to the sense of uprightness and is of use in identifying a vestibular component, for example in patients with head injury, in whom vestibular, brainstem disease and trochlear injury may be compounded.

Perception of linear motion

Establishing thresholds for detection of linear motion through an otolithic 'sensation of movement' is difficult because the accelerative forces acting on the body give rise to somaesthetic cues to motion (normal results are summarized in Benson *et al.*, 1986). However, Walsh (1960) showed that subjects with unilateral loss of labyrinthine function showed a consistent and significant insensitivity to linear motion in the lateral direction when lying sideways on a parallel swing with the lesioned side down, in which position lateral acceleration is signalled primarily by the remaining sacculus; whereas in supine or lesioned side up positions they had normal sensitivity to threshold levels of acceleration. Walsh thought that the loss of sensitivity was because the otoliths of the intact sacculus compress the macula in the uppermost ear and lessen its sensitivity to shearing forces.

Otolithic control of eye movements

(i) Ocular counter-rolling responses to slow tilt (Diamond and Markham, 1983) or static tilt (Kirienko *et al.*, 1984) which stimulate the otoliths in the absence of canal signals have been studied in patients with labyrinthectomy with excised acoustic neuroma. The patients have increased asymmetry, inconsistency and spontaneous fluctuations in the ocular counter-rolling, induced by tilt, more so when the intact ear is depressed than when elevated.

In patients with spasmodic torticollis, Diamond *et al.* (1988) consistently found that otolith-induced ocular counter-rolling, evoked by slow roll rotation, did not sustain at extreme positions, with the eyes eventually rolling in the direction of the tilt. This finding is consistent with the emerging concept that the basal ganglia have a modulating influence over vestibular-oculomotor control (*see* Bronstein and Rudge, 1988; Kennard and Lueck, 1989, for reviews).

(ii) Otolithic compensatory eye-movement reflexes exist for vertical (Paige, 1989) and lateral (Baloh *et al.*, 1988; Bronstein and Gresty 1988; Schwarz, *et al.*, 1989) movements but only the lateral otolith-ocular reflex (OOR) has been studied in patients with neuro-otological disorders. The lateral OOR may be evoked in isolation using linear accelerators such as electric cars or parallel swings which may be cumbersome and expensive. Alternatively, a lateral linear motion stimulus may be delivered on a conventional rotating chair by placing the subject with head eccentric and thrust forwards from the axis of rotation, so that chair rotation gives a combined angular and linear head motion (Gresty *et al.*, 1987).

The lateral OOR may be absent or hypoactive in bilateral labyrinthine disease but is intact in patients with unilateral loss of labyrinthine function (Jongkees, 1968; Brooks *et al.*, 1990; Takeda *et al.*, 1990) and thus indicates global otolith function but is without lateralizing value. Patients with lesions of the brainstem, cerebellum or parietal lobes may have weak, absent or asymmetrical OORs so that the test is of value in demonstrating CNS disorder. In some patients the OOR may be deranged with the canal-VOR remaining intact; a dissociation which could distinguish specifically otolithic causes of imbalance (Barratt *et al.*, 1987; Bronstein *et al.*, 1990).

Vestibulo-spinal responses

As with the OOR, EMG responses to falling may indicate otolith hypo-function but do not have lateralizing value in peripheral lesions; their value is in revealing CNS dysfunction as discussed above.

CONCLUSIONS

A sense of how the body is oriented in space and how its component members are aligned is fundamental to any behavioural act. On the earth's surface, amongst the most important entities for orientation are the direction of gravity and the pattern of accelerative forces acting on the body. It is the function of the otoliths to signal gravity and linear accelerating forces and if disease or unusual environments deprives one of an adequate veridical sense of physical forces, movement becomes uncoordinated and a sense of detachment or derealization can develop causing profound psychological disturbances of anxiety and panic. Although the otoliths clearly have such fundamental importance little is understood about how their signals help to create perceptions and control action and, as a consequence, tests of otolith function are crude. As it is not an easy matter to apply a routine 'screen' for otolith function, the clinician should be particularly aware of the possibility of its dysfunction in patients who complain of types of disorientation, vertigo and imbalance suggestive of problems of dealing with sensing and responding to linear motion and uprightness. In this, the clinician's interpretation may be guided by knowledge of the few disorders of the peripheral and central otolith pathways whose signs and symptoms have been described in detail and whose mechanisms have been identified.

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INHERITED PRION DISEASE WITH 144 BASE PAIR GENE INSERTION

1. GENEALOGICAL AND MOLECULAR STUDIES

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SUMMARY

Genealogical and molecular studies were carried out in four families in which early onset dementia is inherited as an autosomal dominant. These studies indicated that the four families derive from four siblings whose parents were born in the late 18th century in South-East England. The disease was found to be closely linked to a 144 bp insertion within the open reading frame of the prion protein (PrP) gene with a maximum LOD score of 11.02 at zero recombination. Within the general population the PrP gene is polymorphic at codon 129 (allele frequency approximately 30% valine, 70% methionine). The insertion in this family is always within a methionine-129 allele. The age at death of affected individuals whose normal allele encoded methionine at codon 129 was significantly lower than those whose normal allele encoded valine. The clinical features which were very variable and the neuropathological findings, which sometimes included spongiform encephalopathy, but which often did not, are described fully in the accompanying article (Collinge *et al.*, 1992).

INTRODUCTION

Creutzfeldt-Jakob disease (CJD) and Gerstmann-Sträussler syndrome (GSS) are fatal neurodegenerative diseases in man which share a number of features. These include spongiform encephalopathy, deposition in the brain of extracellular amyloid plaques containing prion protein (PrP), and experimental transmissibility (Masters *et al.*, 1981*a*; Adam *et al.*, 1982; Prusiner, 1987). Creutzfeldt-Jakob disease is defined clinically as a rapidly progressive dementia (duration <2 yrs) with the variable occurrence of additional features, e.g. myoclonus and cerebellar ataxia, whereas GSS refers to a more slowly progressive cerebellar ataxia (up to 10 yrs or more) with a varying degree of dementia (Masters *et al.*, 1981*a*; Will and Matthews, 1984). Both are of middle age onset. Neuropathologically, CJD is associated with pronounced spongiform encephalopathy and sometimes with amyloid plaques (Masters and Richardson, 1978). In GSS,

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amyloid plaque formation is common especially in the cerebellum while spongiform changes may be slight or absent (Boellaard and Schlote, 1980).

Although the terms CJD and GSS are useful in describing clinical and neuropathological presentations, their use is complicated by the fact that cases which conform to either description may be found in the same family, together with cases which conform strictly to neither but which may share the same genetic basis (e.g. *see* Adam *et al.*, 1982). The importance of PrP in CJD, GSS and related animal diseases (e.g. scrapie) has led to the suggestion that they should all be described as prion diseases (Westaway *et al.*, 1989).

A further complication of this group of diseases is that while the disease entities have the unique features mentioned above, individual cases may not exhibit all these features. For example, a GSS case diagnosed on the basis of its amyloid plaques may have minimal spongiform encephalopathy. Plaques are found in only a proportion of CJD cases (Kitamoto and Tateishi, 1988), and transmission attempts are frequently unsuccessful. As the molecular basis of these diseases becomes clearer, there are grounds for believing that some cases of prion disease have none of the classical features (Collinge *et al.*, 1989, 1990).

Approximately 15% of CJD cases and almost all those of GSS occur in a familial form with autosomal dominant inheritance (Masters *et al.*, 1979, 1981*a*), provoking the question of how a disease which has been shown to be experimentally transmissible to animals can also be inherited. Either what is inherited is a strong disposition to an environmental agent, or the agent itself must be assumed to be host derived (Baker *et al.*, 1985).

A major advance in our understanding of the pathogenesis of prion diseases occurred with the identification of the PrP gene (Chesebro *et al.*, 1985; Oesch *et al.*, 1985). This highly conserved gene, present in a single copy [on chromosome 20 in man (Sparkes *et al.*, 1986)], codes for an ~250 amino acid glycosylated protein that performs an as yet unknown function in the cell membrane. The normal cellular isoform of this protein, PrP^{C}, is degraded by treatment with proteinase K *in vitro*, whereas in prion diseases a proteinase K resistant form accumulates in affected tissue (for review, *see* Prusiner, 1987). This pathological isoform is referred to as PrP^{Sc} or PrP^{CJD} depending on source (Scrapie or CJD affected brain). The difference in structure between PrP^{C} and PrP^{Sc}/PrP^{CJD} is not known but in a variety of experimental procedures the PrP^{Sc}/PrP^{CJD} co-purifies with infectivity, indicating that it is likely to be an integral component of the transmissible agent. Numerous experiments have failed to demonstrate the presence of infectivity-specific nucleic acid suggesting that PrP^{Sc}/PrP^{CJD} may be the only component of the transmissible agent. One possibility is that the PrP^{Sc}/PrP^{CJD} isoform carries the ability to convert the normal protein PrP^{C} into the proteinase K resistant form. Possible mechanisms for this have been discussed by Weissmann (1991).

Of particular interest is the recent discovery that some families with CJD or GSS carry mutations within the open reading frame (ORF) of the PrP gene. A number of such mutations have now been described (*see* Table 1).

We report here a genealogical and molecular study of those patients with a 144 bp insertion within the ORF of the PrP gene. They are all members of a large pedigree in which a fatal neurodegenerative disease occurs in an autosomal dominant pattern, some cases of which conform to the clinical and neuropathological definition of CJD.

In the accompanying paper (Collinge *et al.*, 1992) we report the clinical findings on these patients and review the clinical reports on earlier family members in an attempt to define the boundaries of phenotypic expression of this PrP gene mutation.

TABLE I MUTATIONS WITHIN THE PrP GENE IN CASES OF CJD AND GSS

Codon	*Changes*	*References*
51–91	144 bp insertion	Owen *et al.*, 1989
102	Proline → leucine	Hsiao *et al*, 1989
117	Alanine → valine	Doh-Ura *et al.*, 1989
200	Glutamic acid → lysine	Goldgaber *et al.*, 1989 Goldfarb *et al.*, 1990*b,c*
178	Aspartic acid → asparagine	Nieto *et al*, 1991
51–91	216 bp insertion	Owen *et al.*, 1991
51–91	168 bp insertion	Brown *et al.*, 1991

MATERIALS AND METHODS

Molecular analysis

DNA was extracted from peripheral blood, lymphocytes or CNS tissue using standard techniques The presence of the 144 bp insertion was demonstrated by the use of the polymerase chain reaction (PCR) to amplify the entire ORF of the PrP gene (Owen *et al.*, 1990*b*), and the results confirmed by Southern blot analysis of genomic DNA digested by the restriction enzyme, Msp-1 or Dde-1, using a human PrP cDNA probe.

The amino acid polymorphism at codon 129 of the PrP gene, a methionine (M) to valine (V) substitution resulting from an adenine to guanine transition, we investigated by allele specific oligonucleotide (ASO) hybridization to amplified genomic DNA as described in Owen *et al.* (1990*a*).

For sequencing the 144 bp insertion, amplified DNA of the mutant allele was cloned and at least three recombinant clones sequenced on both strands by the method of double stranded DNA sequencing (Chen and Seeburg, 1985) with primers as described previously (Owen *et al.*, 1990*b*).

Subjects

Blood was collected from a number of patients attending hospitals in the London area where they were being investigated for presenile dementia. These samples were screened for the known mutations in the ORF of the PrP gene as part of a survey of atypical dementias (Owen *et al.*, 1991). Insertions of 144 bp were identified in the PrP ORF of several individuals who were members of four apparently unrelated families.

Genealogical investigations

Family lineages were traced back from affected probands. Birth certificates were obtained for each from the office of the Registrar General of Births, Deaths and Marriages (St Catherine's House, London) thus identifying the parents and enabling a search to be made of the marriage index. The marriage certificate gave information on ages, residence, condition, occupations, woman's maiden name and also the proband's grand-parental (male) names and their occupations. Searches could then be made for births of siblings of the original proband (after 1911 the birth index also includes the mother's maiden name) and deaths of the parents. Death certificates gave information on age, place of death, cause of death and informant's description and residence. The age of death enabled searches to recommence with the birth index Working from this and subsequent information, lineages were traced back to 1837 when registration commenced. Local parish records were consulted for information prior to this date. Use was also made of the census records (1841 – 1881 at 10-yearly intervals) currently available for inspection at the Public Records Office, Chancery Lane, London. These list the names, ages (only approximate in 1841), relationships, occupations and places of birth for all individuals staying at a particular address on the census night. These were useful for identifying siblings' names and occasionally family relationships not formally registered.

Where individuals died in hospital or other institutions, original case notes were obtained whenever possible. These provided, in addition to clinical detail, information on other family members. Other sources of information included county archivists, medical records offices and coroners' reports.

RESULTS

Genealogy

The genealogical investigation showed that the four families which were originally thought to be independent of each other did in fact derive from a sibship born to a couple living in South-East England in the early 19th century. Dementing illness has been tracked forward from this sibship to the probands (*see* Fig. 1). A description of all these cases is presented in the accompanying article (Collinge *et al.*, 1992). Illness was confirmed (cases with filled symbols, Fig. 1) by satisfying the following criteria: death in middle age, and at least one of the following: (i) death certificate indicating neurodegenerative disease; (ii) case notes indicating neurodegenerative disease or dementia; (iii) death in an asylum or mental hospital. For the five remaining cases in Fig. 1, the illness was unconfirmed because of failure to satisfy the above criteria, untraced death certificate, or death before the normal age at onset. However, except for Case VII 15, all these cases are obligate carriers.

It has not proved possible to deduce which of the founders I1 or I2 was the affected

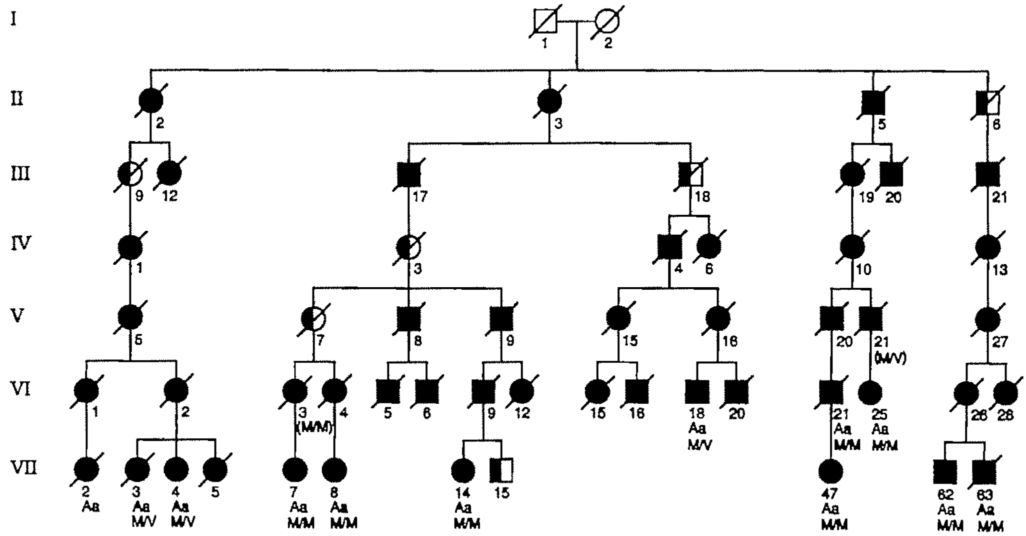

FIG 1 Pedigree of family Unaffected individuals are not shown Closed symbols are affected cases based on a diagnosis of dementia. Half-closed symbols are probably affected cases where data are incomplete. *See* Collinge *et al.* (1992) for full pedigree and full description of each case. Haplotypes: A = mutant allele, a = normal allele; M = Methionine^{129}; V = Valine^{129}. Codon 129 genotypes in parentheses are inferred from typed offspring For reasons of confidentially not all genotypes on which the linkage analysis was performed are illustrated Full details of allelic assignments on which the LOD scores are based will be made available to investigators for scientific purposes only and in strict confidence

person. I1 died at age 50 in 1844 from 'inflammation of the chest'. His wife, I2, did not appear on the 1841 census with him or on later returns which suggests that she may have died or been institutionalized between 1834 (the birth of her youngest child) and 1841 (aged approximately 40 yrs).

Molecular analysis

The results of the molecular analysis are presented in Table 2 which shows the pedigree number of the individuals tested, the method of testing and the assignment of M^{129} and V^{129} alleles. It has already been shown that in all cases the insertion is found within an M^{129} encoding allele (Owen *et al.*, 1991) so the individuals carrying the insertion have genotypes of either M/M or M/V. The 144 bp insertion was sequenced in four individuals (including one asymptomatic carrier) representing the four branches of the main pedigree. In each case the sequence was identical to that originally reported (Owen *et al.*, 1990*b*). The normal PrP contains five uninterrupted repeat sequences spanning codons 51–91. The insertion is in-frame and encodes a further six repeats resulting in 11 uninterrupted repeat sequences. The essential difference between the normal and mutant allele is tabulated in Owen *et al.* (1990*b*). Apart from the first repeat, both of normal and mutant alleles, the amino-acid sequence of the repeats is identical in all respects, although they can be distinguished from each other by their nucleotide sequences. The repeats in the normal allele have been abbreviated to R_1 R_2 R_2 R_3 R_4 and the mutant allele to R_1 R_2 R_2 R_2 R_3 R_2 R_3' R_2 R_2 R_3 R_4. R_3' contains sequence both from R_2 and R_3. The remaining sequence of the ORF of the mutant allele was identical to that previously reported (Kretzschmar *et al.*, 1986). This insertion cannot have resulted

TABLE 2 INDIVIDUALS WITH THE 144 BASE PAIR INSERTION WITHIN THE PrP ORF

Case	*SB*	*PCR*	*Sequenced*	*Codon 129 in normal allele*
V 20*				
V 21**				V
VI 3**				M
VI 18		√		V
VI 21	√	√		M
VI 25	√	√		M
VII 2		√		
VII 3	√	√	√	V
VII 4	√	√		V
VII 7	√	√		M
VII 8	√	√		M
VII 14	√	√	√	M
VII 47	√	√		M
VII 62	√	√	√	M
VII 63	√	√		M
A***	√	√	√	M

144 bp insertion detected by Southern blot (SB) or PCR *This case must have had the insertion since his widow did not and his son did. **The codon 129 genotype of these cases were inferred from typed offspring. ***This is an asymptomatic carrier who cannot be identified for reasons of confidentiality.

from a single recombinational event, and complex duplication and perhaps deletion may have occurred to achieve the observed arrangement.

The discovery of a 216 bp insertion encoding nine extra octapeptide repeats in a pedigree originating from an area in close proximity to the area of origin of this pedigree (Owen *et al.*, 1991), as well as the report of an American pedigree of English descent carrying a 168 bp insertion encoding seven extra octapeptide repeats (Brown *et al.*, 1991), raises the question of genetic instability in these mutations. However, our genealogical studies have demonstrated that the 144 bp insertion appears to have remained stable over at least six generations. Further characterization of the PrP gene may make further haplotyping of these pedigrees possible, which may eventually answer this question unequivocally.

Genetic linkage

Genetic linkage analysis was carried out in the family using MLINK from the LINKAGE program package (Lathrop and Lalouel, 1984; Lathrop *et al.*, 1984). We assumed that the disease followed an autosomal dominant mode of inheritance with age-dependent penetrance. Age at onset was estimated for all affected cases where sufficient information was available. Cumulative numbers of cases affected by increasing age were plotted to estimate penetrance at particular ages in the family. This gave the following age-dependent penetrance values: 10.3% (21–25 yrs); 24.1% (26–30 yrs); 51.7% (31–35 yrs); 86.2% (36–40 yrs); 93.1% (41–45 yrs); 96.6% (46–50 yrs); 100% (51–55 yrs). Under these conditions the LOD score will be decreased by asymptomatic individuals carrying the insertion who are older than the minimum age at onset (age 21 yrs or above). A disease gene population frequency of $q = 10^{-6}$ has been used in this analysis. Even for values of q as high as 10^{-4}, the LOD scores shown in Table 3 are essentially unchanged.

The population frequency of the insertion, p, is of considerable importance in the analysis, since all but one married-in spouses have not been genotyped. However, none of over 100 normal Caucasian controls carried the insertion. Even with a value of $p = 10^{-2}$, a LOD score in excess of 10 is obtained.

The maximum LOD score (11.02 at a recombinant fraction of zero) is highly robust to changes in other linkage variables. If a maximum penetrance of 95% is used in the analysis, the score is reduced to 10.98. The possibility that a person carrying the insertion is in fact suffering from another dementing illness is low because alternative causes

TABLE 3 LOD SCORES FOR THE FAMILY FOR VARIOUS VALUES OF *P*, THE FREQUENCY OF THE INSERTION MUTATION

	Recombination fraction			
P	*0*	*0.05*	*0.1*	*0.20*
10^{-2}	10 02	9 32	8 50	6 62
10^{-3}	10.90	10.20	9 37	7 45
10^{-4}	11 01	10.30	9 47	7.55
10^{-5}	11 02	10.31	9 49	7 56

The population frequency of the disease gene, q, is assumed to be 10^{-6} LOD scores are essentially unchanged with $q = 10^{-4}$

of dementia with this age at onset are also extremely rare. However, the data have also been analysed with the addition of a phenocopy rate (age independent) of 10^{-2}. This reduces the maximum LOD score to 10.98. The results in Table 3 therefore demonstrate highly significant, tight linkage between the disease and genetic marker locus.

Age at onset and death

The factors which determine age at onset and death in the dominantly inherited neurodegenerative diseases are not known but generate considerable interest. Different diseases have different mean ages at onset, e.g. familial Alzheimer's disease compared with Huntington's disease (Masters *et al.*, 1981*b*; Ridley *et al.*, 1988), while different families with the same disease may also show significantly different age at onset distributions (Ridley *et al.*, 1991; Van Duijn *et al.*, 1991). The age at onset may not be normally distributed and may, for example, follow a bimodal pattern (Ridley *et al.*, 1988).

The mean age at death for sporadic cases of CJD is 57.8 yrs ± 9.6 SD and for familial CJD is 51.1 yrs ± 9.6 SD (Masters *et al.*, 1981*b*). We have argued that the age at onset of idiopathic (i.e. sporadic and familial) transmissible dementia is genetically determined (Ridley *et al.*, 1986).

Now that the molecular basis of the familial prion diseases is being clarified, it has become apparent that while different mutations within the PrP gene are associated with different disease characteristics, including duration of symptoms and age at onset (Hsiao and Prusiner, 1990), there is considerable variation in presentation of disease for each mutation and overlap between the presentations of each mutation. With these points in mind an analysis was made of the age at death of affected individuals in this pedigree. These data were available for 35 cases whose death was thought to have occurred as a direct consequence of the illness (excluding accidental death and suicide). Using maximum likelihood estimate procedures the best fit for the age at death distribution was obtained from two normal distributions with equal standard deviations (*see* Fig. 2). This gave a significantly better fit than one single normal distribution (maximum likelihood $\chi^2 = 13.1$, d.f. $= 2$, $P < 0.01$). Parameter estimates suggested that 26% of cases fell into a 'late' age at death group (mean 56.9 yrs ± 3.47 SD) and 74% comprised an 'early'

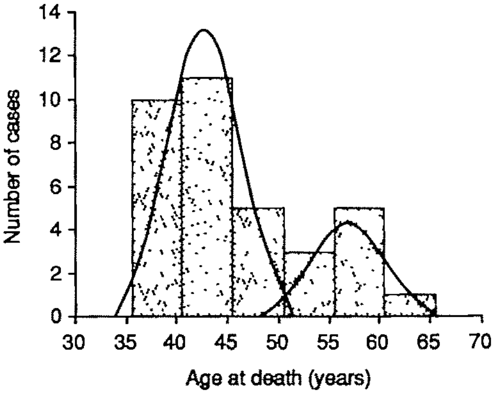

FIG 2 Age at death distribution Histogram shows number of cases with age at death within each 5 yr period Smooth curves are best fit normal distributions

age at death group (mean 42.7 yrs ± 3.47 SD). We designated those who died under age 50 as 'early' death and the remainder as 'late' death.

One view of the pathogenesis of prion diseases is that the post-translational conversion of normal PrP^{C} to the abnormal form PrP^{CJD} is triggered or enhanced by the presence of PrP^{CJD}. In experimental studies using transgenic mice it has been demonstrated that ease of transmission and duration of incubation period are controlled by the sequence homology between the PrP^{Sc} used to transmit disease and the host PrP^{C} (Prusiner *et al.*, 1990). It is possible therefore that the extent to which protein encoded by the normal allele at the PrP locus enters into the disease process in familial prion disease depends upon the sequence homology between the normal and disease related alleles. We therefore asked whether amino-acid polymorphisms encoded in the normal allele could have influenced age at death in this pedigree. The common polymorphism at codon 129 in the PrP gene (frequency 0.68 methionine (M^{129}), 0.32 valine (V^{129}) in Caucasians; Owen *et al.*, 1990*a*) is a candidate in this respect.

In 13 patients for whom data were available (Table 2), the normal allele encoded V at codon 129 in four cases and M in nine cases, the insertion always being within an M^{129} encoding allele. All four with a V^{129} encoding normal allele belonged to the 'late' death group (two died over age 50 yrs and two are alive but over age 50 yrs). Of the nine with M^{129} encoding normal alleles, six were assigned to the 'early' death group (three died under age 50 yrs and three are currently below age 35 yrs and severely ill). This association between M/V genotype and age at death is significant (Fisher's exact $P = 0.0096$, two-tailed). The remaining three affected individuals with M^{129} encoding normal allele had an age at onset between 30 yrs and 35 yrs and are currently moderately or severely affected. They were not included in this statistical analysis because, since in this family the current maximum known duration of illness is 14 yrs, we could not be certain that they would die before age 50 yrs. If all three were to survive beyond age 50 yrs, the significance level would reduce to $P = 0.098$, two-tailed, but if any die before age 50 yrs the current significance level will be enhanced. Although the sample size is small, it would appear that the protein encoded by the normal allele may influence whether death is 'early' or 'late'.

We also looked at age at onset in this pedigree although it could be ascertained for only 29 cases. Maximum likelihood estimates suggested that the best fit for age at onset data was a normal distribution (mean 35.4 yrs ± 7.4 SD). However, ages at onset for three cases with V^{129} encoding normal alleles were >40 yrs, while ages at onset for eight cases with M^{129} encoding normal alleles were <40 yrs. One case with a V^{129} encoding normal allele and one with a M^{129} encoding normal allele had ages at onset of 40 yrs. Thus there is a significant relationship between M/V genotype and age at onset (Fisher's exact $P = 0.014$, two-tailed). We were unable to assess the relationship between M/V status and duration of illness since these data were often not available for the same cases. It would seem probable, however, that the bimodal distribution of ages at death seen in this pedigree results from a slightly older age at onset and a slightly longer course of illness in those with a V^{129} encoding normal allele.

DISCUSSION

Creutzfeldt-Jakob disease was first shown to be transmissible to primates by Gibbs *et al.* (1968). The existence of forms of CJD with a familial distribution and occasional overlap with the GSS suggested that the latter condition might also be transmissible and this has been shown to be the case (Masters *et al.*, 1981*a*; Tateishi *et al.*, 1984; Baker *et al.*, 1985). The distribution of disease phenotype within the present pedigree, although it includes cases that might be designated either diagnosis, does not correspond overall to either prototypical picture [*see* Collinge *et al.* (1992) for further discussion on this point]. Attempts to transmit disease from a single case in this pedigree have not been successful. Fresh frontal cortical tissue collected at autopsy from Case VI 21 was homogenized in saline and inoculated intracerebrally into common marmosets using our established method (Baker *et al.*, 1985, 1990). These animals remain healthy after more than 5 yrs. In other transmission studies using this species, intracerebral inoculation of brain tissue homogenates from histologically confirmed cases of CJD and GSS have produced neurological disease and spongiform encephalopathy in 20–35 mths (Baker *et al.*, 1985, 1990). We should point out, however, that Case VI 21 did not have marked spongiform changes and that it has been remarked before that ease of experimental transmissibility may be correlated with the degree of spongiform change (Masters *et al.*, 1981*a*). On the other hand, Goldfarb *et al.* (1990*a*) report transmission from an individual with an insertion within the prion gene, but few details were given. As we have noted before (Owen *et al.*, 1990*b*), the insertion is not within the putative infective part of the PrP^{CJD} molecule but lies within the region that is digested by proteinase K, the enzyme used during purification of the infective fraction. It is therefore of considerable importance to know if the proteinase K resistant residue (PrP 27–30) from affected members in this pedigree is infective. If it is this would suggest that the disease is determined by a sequence alteration elsewhere, other than in that part of the molecule associated with transmissibility in experimental situations. Further studies are required, as material becomes available, to establish the generality and characteristics of transmissibility.

The present and other studies have shown tight linkage between mutations within the PrP gene and the occurrence of familial prion disease (Hsiao *et al.*, 1989). However, there still remains the question of whether these mutations confer susceptibility to an exogenous causative agent or whether they are sufficient in themselves to cause disease. This question has been answered to the satisfaction of the present authors by the experiments of Hsiao *et al.* (1990). In these experiments transgenic mice, which expressed a codon 101 (proline → leucine) mutation, homologous to the codon 102 mutation known to be linked to GSS (Hsiao *et al.*, 1989), were created. At approximately 166 d of age these mice spontaneously developed neurological disease and neuropathological changes consistent with spongiform encephalopathy. It has yet to be demonstrated unequivocally that this spongiform encephalopathy is experimentally transmissible to other animals on primary and serial passage. These and other molecular studies have established that familial prion disease is an autosomal dominant disorder and that the associated PrP gene mutations are pathogenic.

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INHERITED PRION DISEASE WITH 144 BASE PAIR GENE INSERTION

2. CLINICAL AND PATHOLOGICAL FEATURES

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SUMMARY

A large family with autosomal dominant segregation of presenile dementia, and other neurological and behavioural features is described. At various times, family members have carried diagnoses of Alzheimer's disease, Huntington's disease, Parkinson's disease, myoclonic epilepsy, atypical dementia, Pick's disease, Creutzfeldt-Jakob disease and Gerstmann-Sträussler syndrome. Molecular genetic studies have enabled classification of this disease at the molecular level as one of the group of inherited prion diseases. Here we describe the phenotype of inherited prion disease (PrP 144 bp insertion).

INTRODUCTION

Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS) and kuru represent the human transmissible spongiform encephalopathies. Related diseases of animals include scrapie and bovine spongiform encephalopathy. The human diseases have all been transmitted experimentally to various animal species by intracerebral and other routes of inoculation (Gibbs and Gajdusek, 1973) and horizontal transmission in man has occurred via iatrogenic routes (Weller, 1989, for review) and ritualistic endocannibalism (Alpers, 1987, for review). Typical CJD is clinically recognized by the occurrence of a rapidly progressive dementia, usually with onset between 45 and 75 yrs, with myoclonus and an electroencephalogram (EEG) showing characteristic pseudoperiodic sharp wave activity. The clinical course to death is usually <1 yr. Frequent additional features include pyramidal, cerebellar and extrapyramidal signs. Atypical presentations are well recognized.

In GSS, the classic presentation is with a relatively slowly progressive cerebellar syndrome with dementia occurring later and a duration of illness of 3–5 yrs (Cathala

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and Baron, 1987). Neuropathologically these conditions are recognized by the classic triad of spongiform change (affecting any part of the cerebral grey matter), neuronal loss, and proliferation and hypertrophy of astrocytes (Beck and Daniel, 1987). These changes are accompanied by the accumulation in the brain of an abnormal, partly protease resistant, isoform of a host encoded protein, prion protein (PrP), as amyloid. Multicentric amyloid plaques are the pathological hallmark of GSS. GSS usually occurs in a familial context and 15% of CJD is familial (Masters *et al.*, 1979), both showing an autosomal dominant pattern of segregation.

Genetic linkage studies between a leucine substitution at codon 102 of the PrP gene and GSS established GSS to be an autosomal dominant condition (Hsiao *et al.*, 1989). This mis-sense mutation has since been confirmed in several other GSS kindreds and has not been found in a large number of normal individuals (Doh-ura *et al.*, 1989, 1990) suggesting that it may be pathogenic. Transgenic mice harbouring a leucine at the corresponding murine codon spontaneously develop a spongiform encephalopathy, confirming pathogenicity of this genetic variant (Hsiao *et al.*, 1990). Other PrP gene variants seen only in affected or at risk individuals from families with GSS or CJD include a 144 bp insertion and point mutations at codons 117, 178, 198 and 200 (Doh-ura *et al.*, 1989; Goldgaber *et al.*, 1989; Owen *et al.*, 1989; Goldfarb *et al.*, 1991; Prusiner, 1991). Formal confirmation of genetic linkage between the 144 bp insertion and the disease has now been achieved (Poulter *et al.*, 1992). The observations in the transgenic model of codon 102 disease, combined with the occurrence of these genetic defects only in families with spongiform encephalopathies, implies that these other mutations are also almost certainly pathogenic. The identification of one of these mutations in an affected individual from a family with a neurodegenerative disease enables a molecular diagnosis of CJD/GSS or inherited prion disease to be made (Collinge *et al.*, 1989, 1990). Diagnosis can now thus be based at the DNA level. Screening of numerous patients with dementia and/or ataxia, including a large number not thought on clinical grounds to be CJD/GSS, led to the identification of additional cases with the 144 bp insert type of inherited prion disease which are now demonstrated to form part of a large kindred with variable clinical and pathological features. Here we present these observations and define the phenotype of inherited prion disease (PrP 144 bp insertion).

PATIENTS AND METHODS

Information on 47 affected family members (with varying degrees of detail) has been collected. This ranges from simple data such as cause of death given on death certificates obtained from public records, or in some cases merely the fact that the patient died in a mental hospital, to a comprehensive clinical, investigative and pathological assessment. Sources include death certificates, asylum records, hospital case notes, coroner's inquest reports and interviews with relatives. Many of the living affected or recently deceased patients were examined by one of us (J.C., A.E.H., M.M., M.N.R., T.J.C.) Cases VII.7 and VII.8 were the subjects of a previous report (Collinge *et al.*, 1989).

Neuropathological reports are available on four cases. Two of these cases have been reported previously (V.20, Meyer *et al.*, 1954; VII.63, Collinge *et al.*, 1990).

RESULTS

The pedigree is shown in Fig. 1. This is incomplete in that the offspring of individuals not known to be affected in earlier generations are not shown. Full case reports are given in the Appendix.

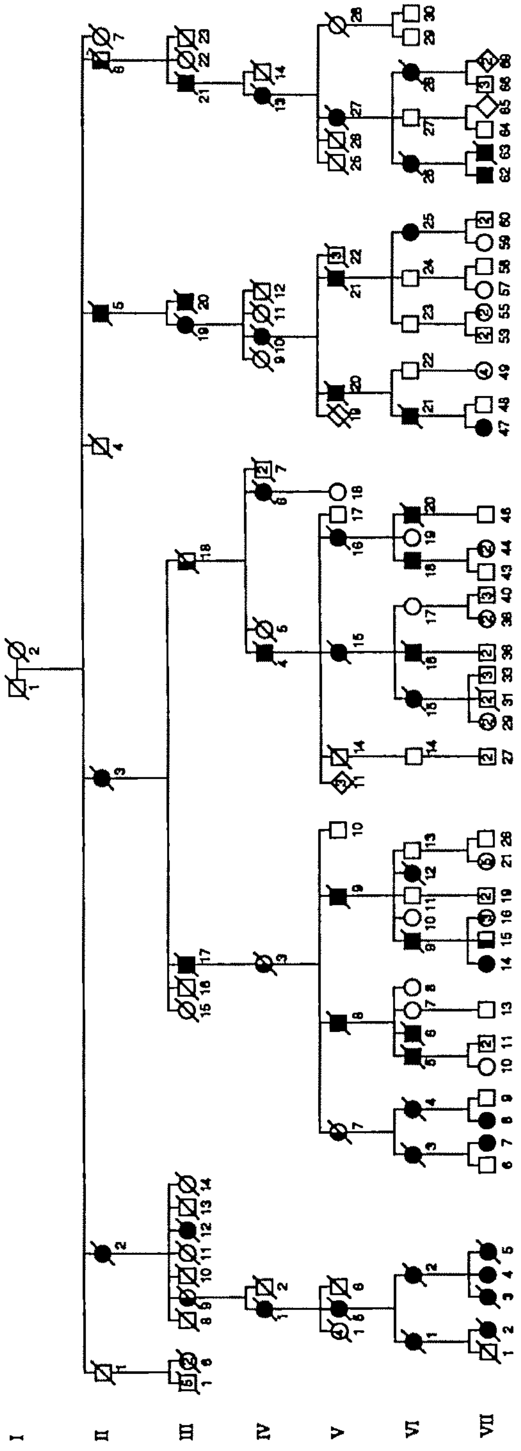

FIG 1. Pedigree: squares are males, circles are females, diamond indicates sex unknown. Shaded symbol indicates affected, half-shading indicates probably affected (definite clinical information was not available). Numbers within symbol indicate numbers of individuals. Slashed symbol indicates person deceased.

The principal clinical features of the illness are given in Table 1. In many cases in earlier generations information was not available with respect to many of these features. The central clinical syndrome is a uniformly progressive cortical dementia. Early in

TABLE 1. CLINICAL FEATURES IN AFFECTED FAMILY MEMBERS

Case	*Sex*	*Age at onset (yrs)*	*Age at death (yrs)*	*Premorbid personality disorder*	*Personality changes (aggressive depressed)*	*Progressive cortical dementia*	*Myoclonus*	*Pyramidal signs*	*Cerebellar ataxia dysarthria*	*Extrapyramidal features*	*Seizures*	*Chorea*
II.2	F		47			+						
II.3	F		61			+		(+)				
II.5	M	32	36		+	+						
III.12	F		62			+						
III.17	M	36	39			+					+	
III.19	F	38	44		+	+		(+)	(+)			
III.20	M		37			+						
III.21	M		39			+						
IV.1	F		42			+						
IV.4	M	39	57			+						
IV.6	F	39	40			+	(+)	+	(+)			
IV.10	F	26	39		+	+	(+)	+	+	+	+	
IV.13	F		54		+	+				+		
V.5	F		46			+						
V.8	M		56			+						
V.9	M		35			(+)						
V.15	F	32	43			+					(+)	
V.16	F	53	57	+	+	+	+		(+)			
V.20	M	36	38		+	+		+	+			
V 21	M	48	52			+		(+)	+	+		
V.27	F	38	46	+	+	+	(+)	+	+	+		+
VI.1	F		53			+						
VI.2	F		46			+			+			
VI.3	F	28	37			+		+	+		+	
VI.4	F		44			+						
VI.5	M		40			+						
VI.6	M		46	+		+		+	+	+		
VI.9	M		43			+						
VI.12	F		46			+						
VI.15	F		41			+	(+)					
VI.16	M	39	48	+		+		+	0			
VI.18	M	43		+	0	+	0	0	0	0	0	0
VI.20	M	34	43	+	+	+			(+)			
VI.21	M	40	45		+	+	+	0	(+)	0	0	+
VI.25	F	33				+		0	(+)			+
VI.26	F	32	41	+		+		+	+			
VII.2	F	34	43		+	+	+	0	+	0	+	
VII.3	F	40	53	0	+	+	+	(+)	+	+		
VII.4	F	47		0	0	+	0	0	0	0	0	0
VII.5	F	37	45			+	+					
VII.7	F	23		0	0	+	+	(+)	+	0	0	0
VII.8	F	22		0	0	+		+	+	0	0	0
VII.14	F	32			+	+		(+)				
VII.15	M					+						
VII.47	F	23		0	0	+	0	0	0	0	+	0
VII.62	M	35		+	+	+	0	0	+	0	0	0
VII.63	M	24	36	+	+	+	0	+	+	0	+	0

+ = present; 0 = absent; (+) = equivocal; blank = information not available the course focal features (e.g. dysphasia) may predominate but the dementia inevitably becomes generalized. Memory loss is invariably present eventually but memory may be relatively spared early in the clinical course (e.g. VII.7).

Of considerable interest is the presence of a premorbid personality disorder in a number of cases. A history of this was not usually available in early generations. Family members frequently give a vivid description of long-standing personality difficulties predating neurological onset in their affected relatives. In several cases this personality defect has been recognized from early childhood and contrasts sharply with that of their unaffected siblings who were of apparently normal personality. The characteristic features of this personality disorder are aggression, irritability with short temper, anti-social and criminal activity and hypersexuality. Illegitimacy is strikingly common in this pedigree. Increasingly aggressive behaviour, associated with depression and suicidal attempts, was commonly seen accompanying the early dementia.

Additional neurological features include myoclonus, which occasionally was of sufficient severity to throw the patient to the floor. However, these occurred in a minority of patients, and myoclonus was sometimes subtle. Pyramidal signs are frequent but spasticity is unusual, except in terminal stages of the illness. Cerebellar ataxia and dysarthria are common in the later stages of the illness, but during the early stages ataxia is frequently absent or manifest only by a slightly broad-based gait. Definite extrapyramidal features were documented in six cases. Coarse tremor and postural tremors have been noted. In one, the presentation was with features of parkinsonism, and in another, myoclonic epilepsy. Generalized seizures have been observed in five additional patients. Of particular interest is the observation of chorea in three patients and 'athetoid movements' in one additional patient. An homonymous hemianopia was noted in one patient. One patient died of cerebral thrombosis and additional family members have died with cerebrovascular events at a relatively early age; in two individuals cerebral angiomas were diagnosed.

Routine investigations

Biochemical, haematological, serological and endocrine tests were within normal limits with the exception of a single patient with raised serum transaminases and another with a raised alkaline phosphatase. Examination of cerebrospinal fluid (CSF), when performed, was normal.

Electroencephalography

Although EEG recordings were usually abnormal, in no case was the classic pseudoperiodic activity of CJD described. Brief summaries of individual findings are given in the appropriate case histories.

Neuroimaging

Computerized tomography (CT) scans were available in 10 patients and magnetic resonance imaging (MRI) scans in two. The findings varied from normal appearances to moderate (Fig. 2) to severe cerebral atrophy. No specific features were apparent. Positron emission tomography (PET) was performed on one patient and demonstrated cerebellar hypometabolism (P. Tyrell, personal communication).

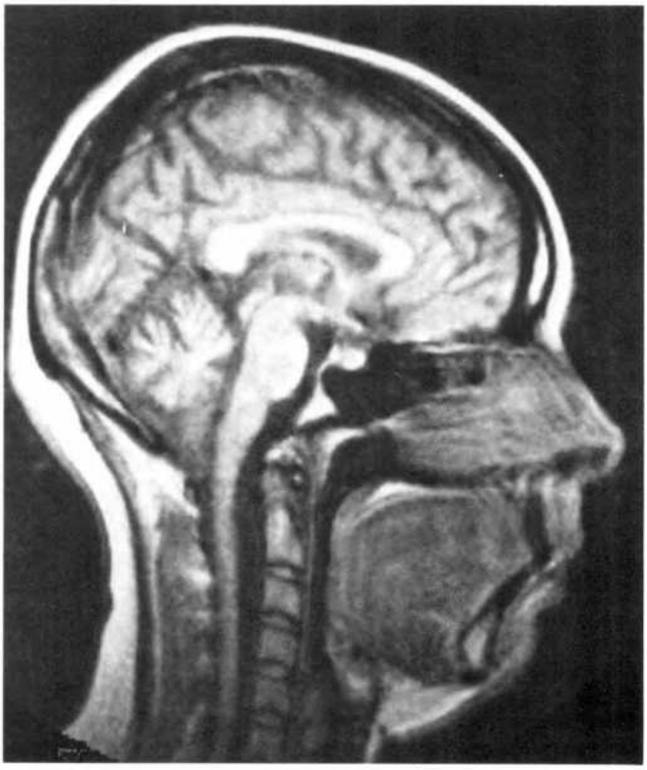

FIG. 2. Magnetic resonance imaging brain scan of patient VII.7 showing moderate cerebral atrophy.

Genetic analysis

Prion protein gene analysis as previously described (Poulter *et al.*, 1992) demonstrated the 144 bp insertion mutation in all affected individuals available for study (patients VI.18, VI.21, VI.25, VII.2, VII.3, VII.4, VII.7, VII.8, VII.14, VII.47, VII.62, VII.63). Tight genetic linkage between this mutation and the disease has been unequivocally demonstrated, confirming that this is an autosomal dominant disorder (Poulter *et al.*, 1992). Although the mutation has been detected in unaffected, at-risk individuals in the family all these individuals are still within the at-risk age group. There is, as yet, no evidence for incomplete penetrance of this disorder.

Pathological findings

The pathological features showed considerable variability. Detailed descriptions are given for four patients. Histological features are summarized in Table 2. Tissue is potentially infectious even following formalin fixation and was handled according to established guidelines [Advisory Group on the Management of Patients with Spongiform Encephalopathy (Creutzfeldt-Jakob disease (CJD), 1981].

TABLE 2 HISTOLOGICAL FEATURES OF AFFECTED CASES

Case	*Sex*	*Age at death*	*Brain weight (g)**	*Atrophy*	*Spongiosis*	*Neuronal loss*	*Astrocytosis*	*Prion plaques*	*β amyloid plaques*
V.20	M	38	1200	+	+++	+++	+++	Not available	Not available
VI 21	M	45	1220 (175)	+	±	−	±	−	−
VII 2	F	43	804 (94)	+++	++	++	++	+	+
VII.63	M	36	1315 (180)	+	−	−	−	−	−

+ mild, ++ moderate, +++ severe, − absent, ± equivocal; *weight of cerebellum and brainstem in parentheses.

Case V.20. This case was studied nearly 40 yrs ago (Meyer *et al.*, 1954). The brain weighed 1200 g. There was marked widening of the sulci over the convexity of both frontal lobes. Atrophy was also present in the post-central gyrus, dorsal parietal lobule, and was most severe in the occipital lobes bilaterally, particularly in the calcarine area. Extensive microscopic examination was carried out.

Histological changes were predominantly cortical, affecting all regions but most severe in the occipital lobes. Status spongiosus was present particularly in the upper layers, with gross disturbance of cytoarchitecture. There was severe neuronal loss, the few remaining cells showing severe shrinkage and pigment atrophy. There was gross astrocytic proliferation. Senile plaques and Alzheimer's neurofibrillary changes were not present. There was no significant change in cerebral white matter with the exception of some lack of myelin in occipital cortex. The basal ganglia, brainstem, cerebellum and spinal cord did not show significant histological change. Tissue was not available for subsequent review of sections with modern immunohistochemical techniques.

Cases VI.21, VII.2 and VII.63. Blocks were taken from the frontal, temporal (including the hippocampus), parietal and occipital lobes, cerebellar hemispheres and vermis, basal ganglia with the sublenticular region containing the nucleus of Meynert, thalamus, pons and medulla oblongata. Sections were stained with haematoxylin and eosin (van Gieson's method), phosphotungstic acid, Congo red and Cresyl violet, using the Luxol Fast Blue technique for myelin and the Marsland-Glees silver stain for axons and nerve cells. Immunohistochemistry was performed using antisera to glial fibrillary acidic protein (GFAP, Dakko), antibodies to the 12−28 fragment of the β A4 protein (from Professor B. H. Anderton) and using antibodies to PrP (from Dr J. Hope and Dr S. B. Prusiner).

Case VI.21. The brain weighed 1220 g and the brainstem and cerebellum 175 g. The leptomeninges were thickened and the sulci were generally mildly widened. Coronal slicing of the cerebral hemispheres showed moderately enlarged ventricles (Fig. 3). There were no obvious abnormalities of the brainstem, cerebellum or upper spinal cord.

Sections showed an excess of hypercellular fibrous tissue in the leptomeninges. There was nothing to relate to the clinical features and no evidence of Alzheimer's disease. However, there was mild, subtle, patchy sponginess and an increased number of astrocyte nuclei in the cerebral cortex. In the deep grey matter as well as in the cortex there were a few small clumps of dark nuclei suggestive of neuronophagia. Some fibrillary glia with corpora amylacea were found deep to the ependyma and to the pial surface. In the cerebellum there were also subtle abnormalities: few single small vacuoles in the molecular layer, pallor of some Purkinje cells and scanty torpedo swellings of their

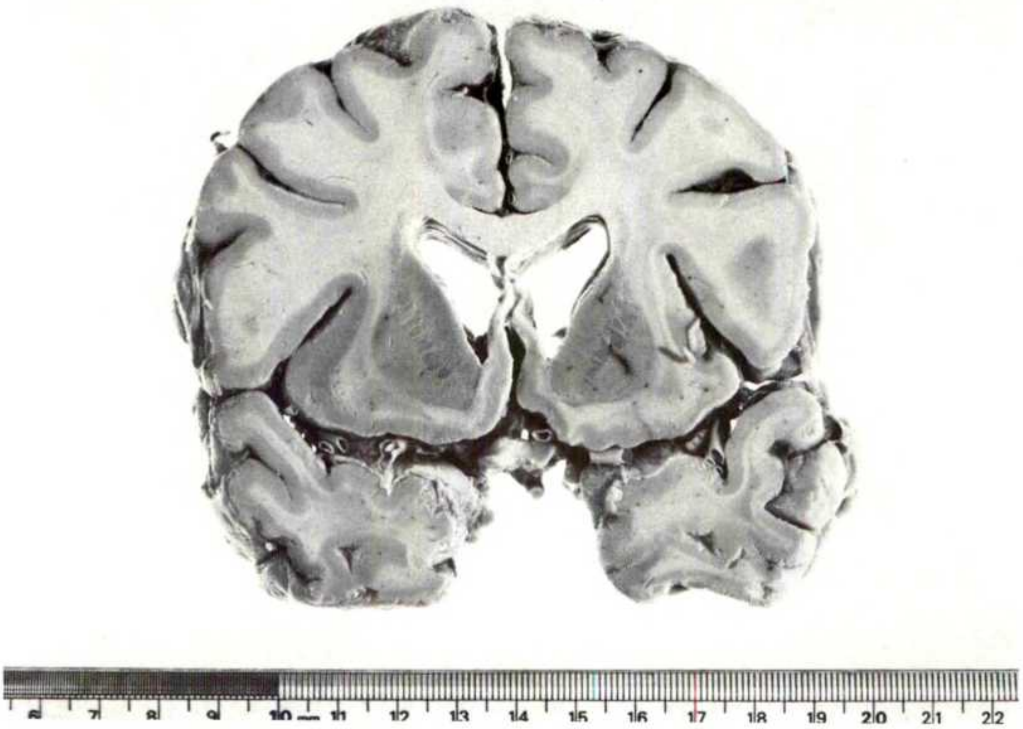

FIG. 3. Coronal brain slice of patient VI.21 showing widened sulci and moderately enlarged ventricles. The ventricular border of the caudate nucleus is flattened.

axons. The appearances were consistent with CJD, but they were surprisingly slight. Immunocytochemical staining to β A4 and PrP were both negative.

Case VII.2. The brain weighed 804 g and the brainstem and cerebellum 94 g after fixation. The leptomeninges were thickened and the cerebral convexities were markedly shrunken with atrophy of gyri, particularly of the frontal, parietal and occipital lobes bilaterally but relatively sparing the temporal lobes. The inferior surface of both frontal lobes and the anterior two-thirds of the temporal lobes were much less atrophic compared with the gyri at the convexity. The sulci were markedly widened. Coronal sections revealed markedly dilated lateral ventricles, including the temporal horns, and somewhat atrophic caudate and lentiform nuclei on both sides along with tiny lacunae in the globus pallidus (Fig. 4). A feature of all slices was an extremely thin, yellow cortical ribbon not restricted to any one arterial territory. Cortical thickness ranged from 0.2 cm to 0.5 cm and it appeared as if the cortex was separated from the underlying white matter. The septum was intact and the hippocampus on both sides was rounded but well demarcated. The thalamus, subthalamic nuclei and red nuclei appeared macroscopically normal. The substantia nigra and locus coeruleus were well pigmented. The aqueduct

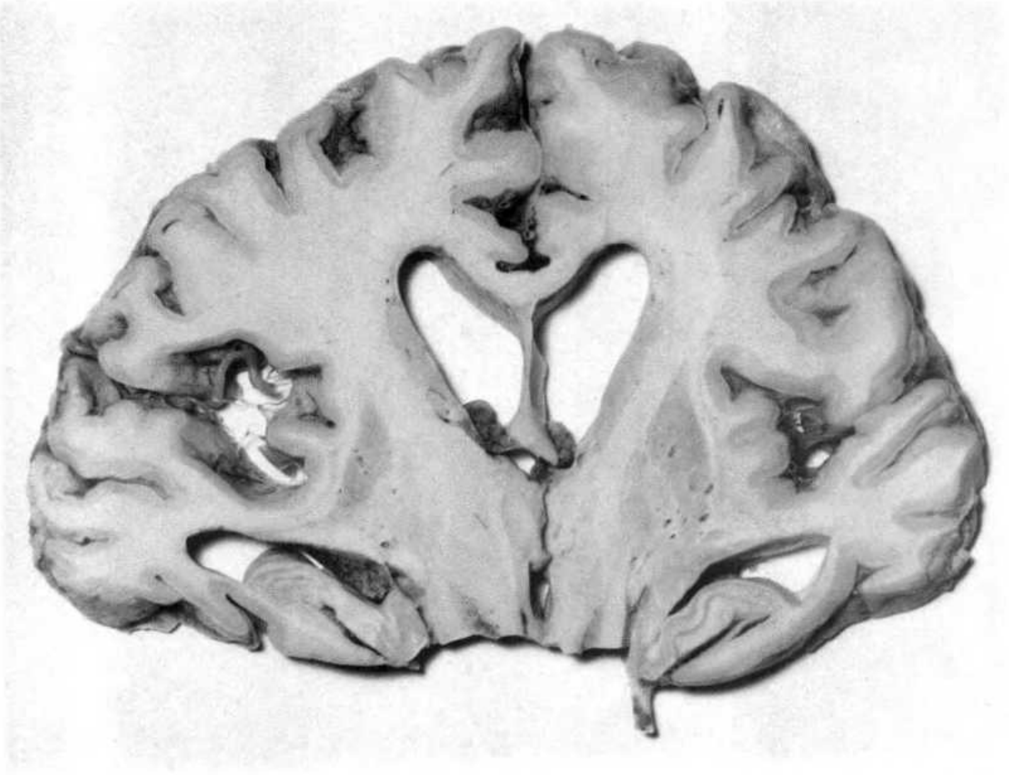

FIG. 4. Coronal section of patient VII.2 showing gross dilatation of the lateral ventricles, atrophy of caudate and lentiform nuclei and lacuni in globus pallidus.

was dilated and measured 0.18 cm. There was extensive atrophy of the cerebellar folia which was more marked in the inferior aspect of the hemispheres and in the vermis.

Sections showed widespread neuronal loss accompanied by severe status spongiosus in the deeper neocortical laminae and in the hippocampus (Fig. 5). In the cerebellum the dentate nuclei were relatively preserved but there were profound changes in the cortex with patchy loss of Purkinje cells and atrophy of the molecular and granule cell layers with variable astrocytosis. In addition, scanty but definite congophilic plaques were seen in the molecular layer. These plaques showed a characteristic Maltese cross appearance on polarization of Congo red stained sections (Fig. 6). Basal ganglia, periaqueductal grey matter and colliculi, and the cerebral white matter showed intense gliosis. Prion protein immunoreactivity of plaques was demonstrated (Fig. 7) and a small number of the congophilic plaques showed β A4 immunoreactivity (Fig. 8). A histological diagnosis of GSS was made.

Case VII.63. The brain weighed 1315 g and the brainstem with the cerebellum 180 g. There was a slight thickening of the leptomeninges, particularly over the convexity, and there were two orange-coloured scars 1 cm and 0.7 cm in diameter in the left orbital

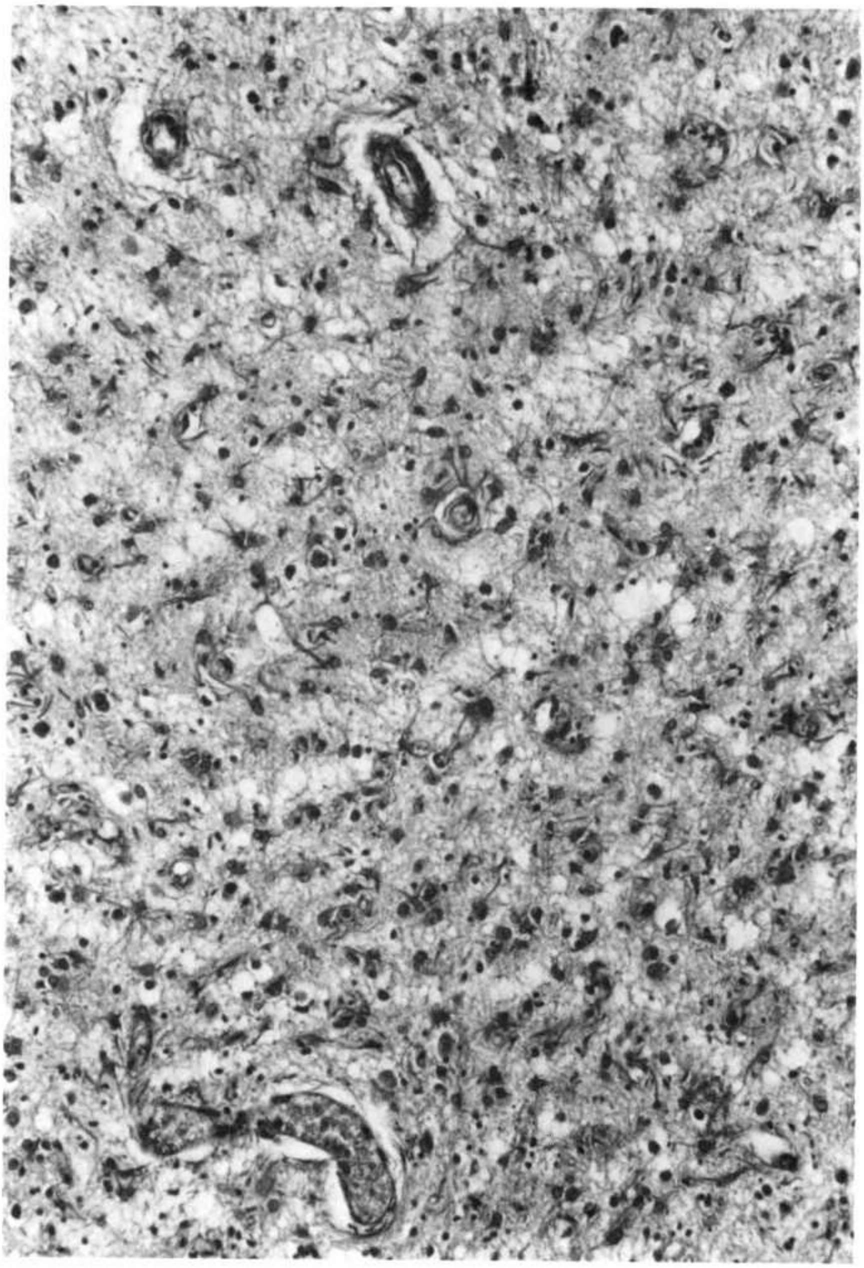

FIG. 5. Phosphotungstic acid haematoxylin stained section of cerebral cortex from patient VII.2 showing hypertrophic astrocytic proliferation and status spongiosus. Magnification ×250.

gyri. The cranial nerves and blood-vessels were normal. The gyri appeared narrowed and Sylvian fissures and many other sulci were widened. The lateral ventricles appeared slightly enlarged on coronal slicing with rounding of their angles (Fig. 9). The

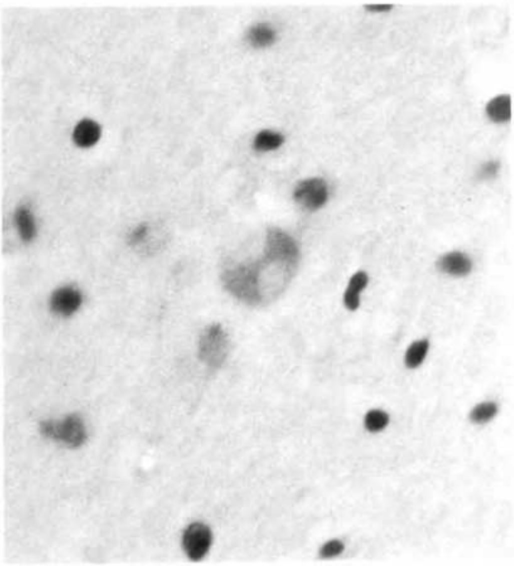

FIG. 6. Maltese cross appearance on polarization of a congophilic plaque in the cerebellar molecular layer of patient VII.2. Magnification ×250.

hippocampus appeared normal on both sides. Substantia nigra and locus coeruleus appeared paler than usual.

Sections revealed no evidence of cortical neuronal loss or gliosis. Dystrophic neurites were not seen. The only abnormality seen in the cortex was a few abnormally large pale nerve cells with eccentric nuclei. There was a moderate increase in the number of astrocytes in the globus pallidus on both sides. Some extraneuronal pigment was seen in the substantia nigra; however, there was little cell loss. A small, old perivascular scar was noted in the left cerebellar hemisphere. Occasional abnormalities (scanty torpedo swellings and swelling of dendrites) and patchy loss of Purkinje cells were seen. The presence of the old contusion in the left orbital region was histologically confirmed. Congo red staining for amyloid was negative. Immunohistochemistry for β A4 demonstrated weakly positive staining in blood-vessels but there was no deposition in the cerebral parenchyma. There were no features of CJD, GSS or Alzheimer's disease. Further sections of cerebellum and cortex were immunostained with antisera to PrP, showing immunoreactivity of Purkinje cells and in some neurons of the superficial laminae of the cortex (Clinton *et al.*, 1990).

DISCUSSION

Both the clinical and pathological features of affected individuals in this family show considerable variability. The clinical phenotype varies from Case V.20 with a rapidly progressive dementia similar in course to classical CJD to that of individuals (e.g. VII.63) in which the clinical course mimicked Alzheimer's disease and in which a long-standing antisocial personality disorder was a prominent feature. However, histories from earlier

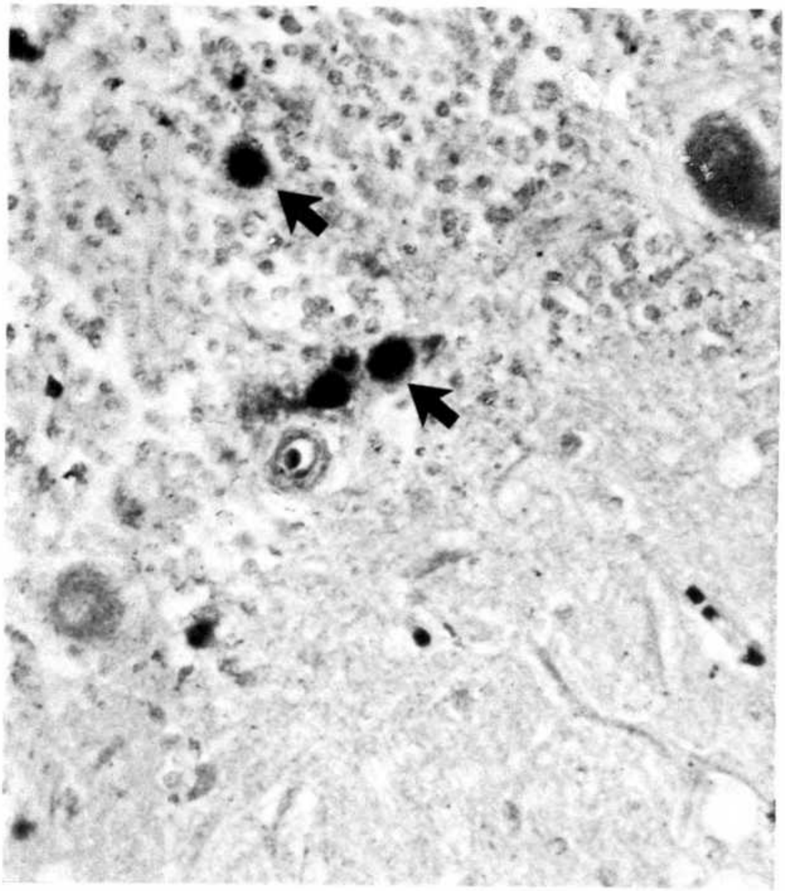

FIG. 7. Prion protein immunoreactivity of amyloid plaques in molecular layer of cerebellar cortex of patient VII.2. Magnification ×350.

generations, which were generally scanty, should be interpreted with caution. The current and preceding generation, on which most detailed information is available, shows a more consistent picture of a long-standing personality disorder, followed in early or mid-adult life by a slowly progressive multifocal dementia preceded by personality changes involving aggression and depression. This was accompanied by a varying combination of cerebellar ataxia and dysarthria, pyramidal signs, myoclonus and occasionally extrapyramidal signs, chorea or seizures.

Apart from DNA analysis, investigations were largely unhelpful in this disorder. Examination of CSF, when performed, was normal. The only routine investigation of diagnostic value in prion disease is the EEG. None of the cases that were so examined had the characteristic EEG described in CJD, although all recordings showed non-specific abnormalities. Neuro-imaging revealed only mild to moderate atrophy. There were no features of diagnostic significance. Functional imaging using PET has so far been performed only on one case.

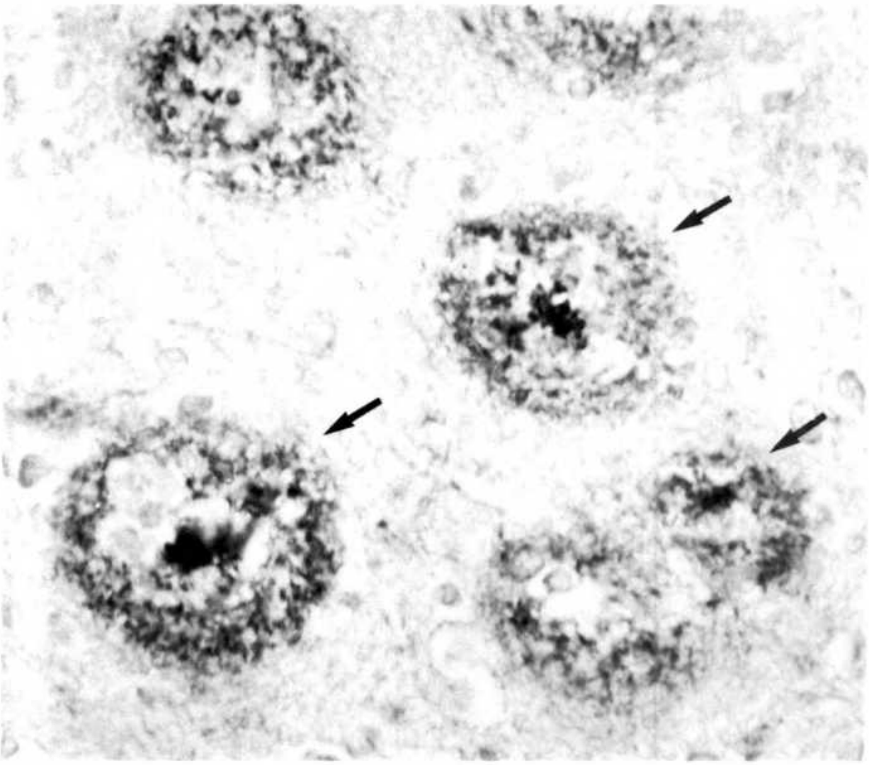

FIG. 8. β A4 immunoreactivity of amyloid plaques in cerebral cortex of patient VII.2. Magnification ×850.

The variation of histological features in the four cases that were examined is remarkable. Case V.20 is used to illustrate classic CJD pathology in Greenfield's neuropathology. At the other extreme, Case VII.63 showed no features of CJD despite extensive histological survey. Prion protein immunoreactive plaques were seen in one patient. Interestingly, β A4 immunoreactive plaques have also been demonstrated in this patient. However, neurofibrillary tangles, reported in inherited prion disease (PrP serine 198) were not seen. In an individual dying from a presenile dementing illness, inherited prion disease (PrP 144 bp insertion) cannot be excluded by routine neuropathology.

This phenotypic variability, ranging from a clinical picture characteristic of classical CJD to that of a GSS-type illness of long duration (exceeding the longest duration published for GSS) and with histological variability from gross spongiform change and PrP plaques to essentially normal appearances in a single family draws into question the usefulness of the terms familial CJD and GSS. Classical subacute CJD and GSS describe ends of a spectrum of phenotypic expression of prion disease. Both syndromes are associated with the accumulation of protease-resistant PrP and the inherited forms have mis-sense or insertional mutations in the PrP gene. Prion disease therefore seems a more appropriate term, with sporadic, inherited and rare iatrogenic forms. Inherited prion disease can further be subclassified according to the mutation in the PrP.

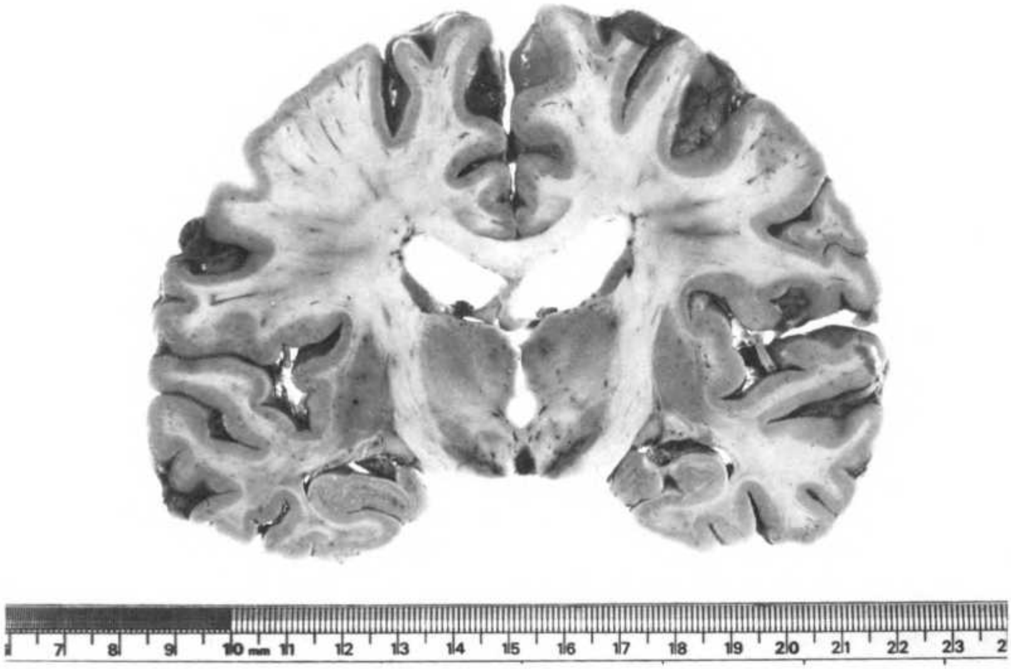

FIG. 9. Coronal brain slice of patient VII.63 showing slight enlargement of lateral ventricles.

Inherited prion disease (PrP leucine 102) was first described in two unrelated families from the US and the UK with neuropathologically confirmed GSS (Hsiao *et al.* 1989) and has subsequently been demonstrated in several other unrelated families (from the US, Germany and Japan) with GSS (Doh-ura *et al.*, 1989; Goldgaber *et al.*, 1989; Speer *et al.*, 1991) including the original Austrian family described by Gerstmann, Sträussler and Scheinker in 1936 (Kretzschmar *et al.*, 1991) and it has been suggested that this genetic subtype correlates with the ataxic type of GSS (Hsiao *et al.*, 1989). However, the larger of the two original codon 102 mutation kindreds shows considerable phenotypic variability at the clinical and histological level (Adam *et al.*, 1982). This variability in inherited prion disease (PrP leucine 102) has recently been confirmed in a German kindred (Brown *et al.*, 1991). Doh-ura *et al.* (1990) report codon 102 mutations in individuals with what they describe as CJD with kuru plaques, although these patients presented with spinocerebellar signs in addition to amnesia and disorientation had a prolonged course.

Inherited prion disease (PrP valine 117) was originally described in a French GSS patient (Doh-ura *et al.*, 1989) and subsequently in a US family of German descent (Hsiao *et al.*, 1991) with presenile dementia associated with pyramidal signs and parkinsonism. This was originally described as familial Alzheimer's disease (Heston *et al.*, 1966) but reclassified as GSS following the demonstration of PrP immunoreactive amyloid plaques (Nochlin *et al.*, 1989). Clinical features in the French (Alsatian) family were presenile dementia with pyramidal and pseudobulbar features, and cerebellar signs in some family members (Warter *et al.*, 1982).

Inherited prion disease (PrP lysine 200), originally described in a sibling pair with CJD (Goldgaber *et al.*, 1989), accounts for the two main ethnogeographic clusters of CJD, in Slovakia (Goldfarb *et al.*, 1990*a*) and in Libyan Jews (Goldfarb *et al.*, 1990*b*). Patients with this subtype of prion disease present with a rapidly progressive dementia and myoclonus and pyramidal, cerebellar or extrapyramidal signs. The duration of illness is usually < 12 mths. Electroencephalography shows the characteristic pseudoperiodic picture seen in classical sporadic CJD. Histological features are usually typical of CJD. Plaques are absent but protease resistant PrP has been demonstrated using immunoblotting (Hsiao *et al.*, 1991).

Inherited prion disease (PrP asparagine 178) was first described in a Finnish kindred with CJD (Goldfarb *et al.*, 1991). This disease presents as a progressive presenile dementia with myoclonus, cerebellar and pyramidal features. The mean duration of illness is around 2 yrs and the characteristic EEG of CJD has not been observed. Histology reveals spongiform change, neuronal loss and astrocytosis but plaques have not been reported. This mutation has now been described in US kindreds of Dutch and Hungarian descent and in a French kindred (Nieto *et al.*, 1991).

Inherited prion disease (PrP serine 198) has been recently described in a US kindred with presenile dementia, ataxia and parkinsonism (Prusiner, 1991). Duration of illness is around 6 yrs. Histology in this family demonstrates numerous neurofibrillary tangles, as seen in Alzheimer's disease, in addition to PrP immunoreactive plaques. Mild spongiform change is also present (Ghetti *et al.*, 1989).

Apart from the 144 bp insertion, two different-sized insertions in the PrP gene have now been reported in inherited prion disease. As with the 144 bp insertion, these consist of different numbers of added repeats of an octapeptide. Goldfarb *et al.* (1990*c*) report an insertion consisting of seven extra octarepeats in a family described as having a bizarre family history of ill-defined neurological illness (Brown *et al.*, 1991). Another insertion consisting of nine extra octarepeats has been described in an individual with late onset dementia and myoclonus (Owen *et al.*, 1991).

Successful transmission of spongiform encephalopathy to experimental animals has been achieved with all the point mutation types of inherited prion disease (except the codon 198 variety) and also with the 168 bp insertion type. Transmission studies have not been attempted with the 216 bp type. Further transmission studies are required with the 144 bp insertion disease. Limited transmission experiments in the marmoset have so far been negative (Poulter *et al.*, 1992).

Of particular interest in inherited prion disease (PrP 144 bp insertion) is the personality disorder which precedes onset of the neurodegenerative illness by many years in some individuals. This has not been described in the other types of inherited prion disease, but this aspect of the history may not have been specifically sought in all these families. It is conceivable that the insertion affects neurodevelopment, in addition to leading to the development of the progressive neurodegenerative disease in early or mid-adult life.

Powerful genetic information is now available for genetic counselling in this condition. The availability of a gene test, rather than a linked genetic marker, demonstrable on DNA extracted from peripheral blood leucocytes enables precise presymptomatic (and antenatal) testing. Presymptomatic testing following rigorous genetic counselling has already been performed (Collinge *et al.*, 1991). In addition, it is possible to assign gene carriers to an early or late age of onset group according to their homozygosity or heterozygosity at PrP codon 129, respectively (Poulter *et al.*, 1992). It remains to be seen if codon 129 genotype influences age at onset in the other types of inherited prion disease. This codon 129 genotype influences age at onset but does not appear to affect the clinical features or pathology. Prion protein gene analysis performed on a routine blood sample should be considered in all cases of presenile dementia (or ataxia). The apparent absence of a family history should not discourage analysis. The full range of phenotypic expression of inherited prion disease has still to be described.

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APPENDIX

Clinical Description of Affected Family Members

Case I.1 Male born between 1794 and 1796. Died age 50 yrs, cause of death 'inflammation of chest'

Case I.2. Female, absent from household at 1841 census. No further details.

Case II.1 Male, born 1815 or 1816 Died age 40 yrs, cause of death 'pneumonia'

Case II.2 Female, born 1817. Died age 47 yrs in psychiatric hospital, cause of death 'decay of dementia'

Case II.3. Female, born 1823 or 1824 (calculated from marriage certificate) Died age 61 yrs (death certificate), or 56 yrs according to marriage record Cause of death 'brain disease and paralysis'

Case II.4. Male, born around 1826 No further details.

Case II.5. Male, born between 1830 and 1832. Admitted to psychiatric hospital at age 34 suffering from dementia for 2 yrs, noted to be aggressive towards his family, to have a failing memory and dull reasoning. Died age 36 yrs, cause of death 'general paralysis of the insane'. No autopsy.

Case II.6. Male, born between 1832 and 1834. Died age 28 yrs, cause of death 'pneumonia'.

Case II.7. Female, born around 1834. No further information

Cases III 1–7. Five males and two females. Born 1841–1854. No further information

Case III.8–11. Born 1839–1848. No further information

Case III.12 Female, born 1850. Married 1867. It is not known if she had children. Died age 62 yrs in a psychiatric hospital. Cause of death (i) 'influenza', (ii) 'senile decay and dementia'

Cases III.13–16. Born 1843–1859 No further information

Case III.17. Male, born 1852. Admitted to psychiatric hospital 1888. Admission notice stated suffering from dementia, 'memory quite gone—he is set and dirty in habits' Well nourished. Died in 1891, cause of death 'decay of epilepsy'. No further details

Case III.18. Male, born 1857. Worked as rag and bone collector, died age 39 yrs in police station, coroner's inquest, cause of death 'disease of heart and lungs accelerated by exposure to the weather'. No further details.

Case III 19. Female, born 1856 She was admitted to psychiatric hospital at age 41 yrs. Husband dated onset of dementia to an episode of post-natal depression at age 38 yrs She had attempted suicide by drowning She had had what were described as fainting fits for several years prior to admission The admission case-book noted that she was weak-minded with a defective memory for recent events and that she was dirty in her habits and required constant attention. Knee-jerks were brisk but plantar responses flexor The diagnosis was recorded as dementia with hereditary predisposition and excited by lactation. The following year she was noted to fall about. She was treated with thyroid extract without effect. She had several falls from a chair and sustained injuries and by age 43 yrs could not walk unaided. She was doubly incontinent. She became bedbound and developed carbuncles and died at age 44 yrs At autopsy the brain weighed 36 5 ounces (1035 g) and the dura was thickened. There was marked cortical atrophy. Histological examination showed degeneration of the pyramids. Arteriole walls were noted to be granular

Case III.20. Male, born 1857. Died age 37 yrs in psychiatric hospital. Cause of death 'general paralysis of the insane and gangrene of lung'.

Case III.21. Male, born 1856 Admitted to psychiatric hospital at age 39 yrs with diagnosis of dementia. Died 3 wks later. Cause of death 'spinal sclerosis'.

Case III.22. Female, born 1857 or 1858. No further information.

Case III.23. Male, born 1859. No further information

Case IV.1. Female, born 1859 Married at age 16 yrs giving false age on certificate Died age 42 yrs in psychiatric hospital Cause of death 'general paralysis of the insane'.

Case IV.2 Male, born 1861. No further information.

Case IV.3. Female, born 1880 or 1881. Died age 47 yrs, cause of death 'uraemia and interstitial nephritis' No autopsy. No details of neurological status.

Case IV.4 Male, born 1880. Worked as railway labourer, onset of dementia sometime after 1918 according to wife Admitted to psychiatric hospital at age 54 yrs and died there at age 57 yrs. Cause of death at autopsy 'cerebral softening and myocardial degeneration', no details of histology.

Case IV.5. Female, born 1880. No further information

Case IV.6 Female, born 1883. Worked as a charwoman. Admitted at age 40 yrs to psychiatric hospital with a 1-year history of progressive dementia On examination emotionally labile with inarticulate drooling speech, gait abnormality, brisk knee-jerks and ankle clonus Noted on the ward to sometimes throw herself to the floor Clinical diagnosis general paralysis of the insane Died of bronchopneumonia at age 40 yrs. No autopsy performed.

Cases IV 7–8. Males, no information.

Case IV 9 Female, born 1888. Died age 42 yrs, cause of death 'cerebral thrombosis'. No post-mortem was performed. No further details.

Case IV 10. Female, born 1890 or 1891. Admitted to psychiatric hospital at age 36 yrs with a diagnosis of dementia praecox. Her husband had first noticed that she was 'strange' at age 26 yrs. On admission she had gross impairment of memory, perception and ideation. Her speech was incoherent. She was unable to dress herself and required supervision to wash and eat. She had been violent at home, throwing furniture around, and had threatened suicide. On occasions she had been found wandering by the police. On examination she had a normal gait. Knee-jerks were brisk but plantar responses were flexor. Wassermann reaction was negative. At age 37 yrs she was said to be developing a spastic paraplegia and dysarthria She walked with short, jerky steps. Tremor of fingers and tongue were noted. Knee-jerks were brisk but there was no ankle clonus and plantar responses were still flexor. Abdominal reflexes were absent. A diagnosis of general paralysis of the insane was reconsidered. One year later she was noted to be always throwing herself around and sustained various injuries. At age 39 yrs she had a febrile episode and had several convulsions She had numerous bedsores Convulsive movements of the head, face and limbs were again noted 3 mths later Further febrile episodes occurred and she became moribund and died age 39 yrs Post-mortem examination was performed and the cause of death 'myocardial degeneration'.

Case IV 11. Female, born 1895. She died in infancy.

Case IV 12 Male, born 1895 Died age 88 yrs cause of death 'cerebrovascular degeneration'

Case IV.13 Female, born 1878 Admitted to psychiatric hospital at age 54 yrs. On admission she was confused and had a severe memory impairment. She was described as tremulous and depressed She had attempted suicide by cutting her throat. On examination there was tremor of hands and tongue. Gait was normal and reflexes present but sluggish. She had chronic bronchitis. She died 2 mths later and a post-mortem examination was performed The cause of death 'myocardial degeneration'. No further details or histology available

Case IV 14 Male, born 1880 No further information

Cases V 1–4 Females, born 1877–1885 No further information

Case V 5. Female, born 1887. Died age 46 yrs Cause of death 'chronic myocarditis and exhaustion from dementia'.

Case V.6. Male, born 1889 No further information.

Case V.7. Female, born 1901 Died age 43 yrs Cause of death toxaemia due to pressure sores over sacrum and hips No details of neurological status Autopsy performed, no details available. Obligate carrier or may have been affected.

Case V.8. Male, born 1905 Died age 56 yrs in a psychiatric hospital. Cause of death 'bronchopneumonia and presenile atrophy'. Autopsy performed, no details available

Case V 9 Male, born 1907. Died age 35 yrs Cause of death 'myocardial degeneration' but he died in a psychiatric hospital

Case V.10 Male, born 1913. Unaffected at age 72 yrs No further information.

Cases V.11–13. Unknown sex No information.

Case V.14. Male, born around 1904. No further information

Case V.15. Female, born 1913. Normal early life and schooling, married age 21 yrs and had three children. Became unable to look after the home at age 32 yrs and had a fall in the street Medical report describes fall as epilepsy but mother did not witness fits. Progressive dementia and died age 43 yrs. No further details

Case V.16. Female, born 1917. Normal childhood and early life Worked in a furniture store and then as a cook Always introverted and nervous Admitted to hospital for investigation at age 53 yrs with a history of progressive difficulty with concentration, memory impairment, anxiety, sleep disturbance and occasional falls On examination she was disorientated in time, had a marked memory deficit, an expressive dysphasia and dyscalculia Neurological examination was otherwise normal. Neuropsychological assessment revealed a severe impairment in all functions tested. A diagnosis of presenile dementia was made She was readmitted at age 54 yrs when she became increasingly aggressive. At age 56 yrs she was noted to have myoclonic jerks and had frequent falls, apparently throwing herself to the floor and often sustaining injury. Her gait was unsteady. She was obese She gradually deteriorated and became doubly incontinent. She developed bronchopneumonia and died at age 57 yrs.

Case V.17. Male, born 1920. No further information.

Case V.18 Female, born 1901. No further information

Case V 19 Sex unknown Born approximately 1907. No further details.

Case V 20 Male, born 1910. He was admitted to a psychiatric hospital at age 38 yrs with a 3-mth history of memory difficulty, poor concentration and being unable to cope with work In addition, he was irritable, developed headaches and deteriorating vision On examination he was confused, disorientated and had memory impairment. Cranial nerves were intact. Tendon reflexes were exaggerated but plantar responses were flexor. Examination of CSF was normal. Serum and CSF Wassermann reaction were negative The following month it was noted that he had pale optic discs and that tendon reflexes were increased on the left He was said to be grossly ataxic. His dementia progressed rapidly and he was thought to have a right homonymous hemianopia. He died at age 38 yrs, 6 mths after onset of symptoms. Of interest, however, is that the post-mortem report notes a 2-yr history of dementia. Neuropathological findings are discussed above.

Case V.21. Male, born 1912. He was admitted to a psychiatric hospital at age 52 yrs with a 3- to 4-yr history of loss of balance, speech difficulty and tremor. He had been treated for Parkinson's disease. On examination he was disorientated, confused and had a memory deficit. Tendon reflexes were generally brisk but worse on the left side. He had cogwheel rigidity and tremor described as of parkinsonian type. Abdominal reflexes were present and plantar responses flexor. A diagnosis of presenile dementia and parkinsonism was made. He died 3 mths later following aspiration of food. Post-mortem examination reported cerebral atrophy. No details of histological examination are available

Case V.22. Male, born 1913 Died within 24 h of birth.

Case V.23. Male, born 1914. Died age 65 yrs. Cause of death carcinomatosis (bilateral carcinoma of tonsils).

Case V.24. Male, born 1916. Died age 43 yrs Cause of death cerebral angioma, confirmed at post-mortem. He had had blackouts for 15 yrs prior to admission to hospital. These episodes were associated with loss of consciousness but not with convulsions and were controlled with phenobarbitone. He collapsed suddenly and died No further details.

Cases V 25–26. Male twins, born 1901. Both died within first year of life.

Case V.27. Female, born 1904. Born prematurely but had normal childhood. Average education and left school at age 14 yrs to work as shop assistant. She is said to have had rheumatic fever at age 16 yrs. She married at age 19 yrs and had three children. Several years later she separated from her husband. She was said to have been involved with numerous other men during her marriage and was apparently untidy, dirty and forgetful. Father and sister reported that she always lacked drive. She moved to London to seek work; occasional letters to her father were described as strange with unusual handwriting. At age 38 yrs she visited her sister who felt that she seemed different and anxious. At age 45 yrs she was admitted to a psychiatric hospital with what was estimated to be a 5-yr history of progressive dementia. She was disorientated with gross memory impairment and loss of intellect. She was euphoric She was said to have marked chorea, ataxia and extrapyramidal rigidity with pyramidal signs. A diagnosis of presenile dementia was made and the possibilities of Huntington's disease or chorea following encephalitis were raised. She was transferred to another psychiatric hospital several months later. On admission she was noted to be dysarthric and to have limb spasticity with an equivocal plantar. A diagnosis of presenile dementia was made The possibility of CJD was considered. Her EEG was diffusely abnormal with some bursts of activity at 5 Hz maximal in the frontal areas but there were no localizing or specific features. On the ward jerky movements of the upper limbs were noted. A repeat EEG 8 mths later was diffusely abnormal. She developed pressure sores and died at age 46 yrs from bronchopneumonia

Case V.28. Female, born 1911. No further information.

Case VI.1. Female, born 1913 Died age 53 yrs. Cause of death stated as extensive burns. Son-in-law describes her as definitely demented, being unable to make a cup of tea or hold a conversation. She died when she poured paraffin on a lit paraffin stove, apparently in an attempt to top it up.

Case VI.2. Female, born 1914. Known to be demented and to have had a gait ataxia. Diagnosis of Huntington's disease. Died age 46 yrs in a psychiatric hospital, cause of death 'cerebral thrombosis'. Post-mortem was performed but no details are available

Case VI.3. Female, born 1926. Puerperal psychosis at age 28 yrs followed by progressive dementia. She had developed an unsteady gait by age 31 yrs. At age 34 yrs she had several generalized seizures. Her speech was slurred and incomprehensible and she was unable to obey commands. There was increased tone in the limbs with hyperreflexia and extensor plantar responses; coordination could not be tested. A ventriculogram showed cerebral atrophy and she died of meningitis and pulmonary embolism shortly after this procedure aged 37 yrs. The brain was not examined histologically.

Case VI.4. Female, born 1927. Died age 44 yrs with dementia. No further details.

Case VI.5. Male, born 1926. Died age 40 yrs in a psychiatric hospital. Cause of death 'bronchopneumonia and presenile dementia'. No further information available.

Case VI.6. Male, born 1928. Normal early development according to mother. He was noted to be backward at school and left at age 14 yrs to work as a van-boy for 6 mths This was his longest period of employment. He did little work between 15 yrs and 18 yrs and then entered the army in 1947, absconding 2 yrs later. He lived at home making no effort to gain employment and became violent towards his father. On one such occasion his father sustained a lacerated scalp and called the police. He was arrested as a deserter and sentenced to 12 mths but was released after 8 mths for good behaviour. He was unable to hold a job for more than a few days. At age 26 yrs he was admitted to a psychiatric hospital. Diagnosis on admission was feeble-mindedness. Psychological assessment indicated a full-scale IQ of 57, verbal scale 67, performance scale 52. He was unable to repeat five digits. He was then cared for by his family until they were unable to cope with his aggressive behaviour and he was readmitted at age 34 yrs under a Section 26 (severe subnormality) order. A diagnosis of Klinefelter's syndrome (confirmed by karyotyping) was noted. On admission there was no evidence of psychosis but he required sedation with chlorpromazine. On examination he was able to give his correct age but little information about his family and home, he had brisk knee-jerks and bilateral extensor plantar responses. Cerebellar dysfunction was not noted. Two months later he was noted to be stumbling on the ward and to have twitching of the eyelids. He held his limbs stiffly and it was felt that he may have cogwheel rigidity of the arms. Six months later his mental state had markedly deteriorated and he required considerable nursing care. He was fumbling in movements with a gait ataxia and frequent falls. Tendon reflexes remained brisk and plantars extensor. Wassermann reaction was negative and haemoglobin, B12 and folate were normal. At age 44 yrs he became bedbound and he was noted to have tremor and rigidity, difficulty swallowing and muscle spasms. He died of a presumed inhalational pneumonia at age 46 yrs. No autopsy was performed

Cases VI.7–8 Females, born 1931 and 1935 No further information.

Case VI 9. Male, born 1925 Died age 43 yrs in a psychiatric hospital. Cause of death 'bronchopneumonia and presenile dementia (Pick's disease)'.

Cases VI 10–11. Female and male, born 1928 and 1930. No further information.

Case VI 12. Female, born 1935. Family member reports had presenile dementia Died age 46 yrs following head injury However, 'diffuse cerebral atrophy' included as cause of death. No further information

Case VI 13. Male, born 1937 No further information

Case VI 14. Male No information.

Case VI 15 Female, born 1936. Presented at age 38 yrs with a severe dementia having been wandering at night confused and was ill-kempt. She had many falls in hospital and scarcely spoke She frequently hurled herself to the floor sustaining injuries. She died suddenly at age 41 yrs after aspirating on a bolus of food. At autopsy the gross appearance of the brain is reported as normal, although no weight is recorded No histology available.

Case VI.16 Male, born 1939 Normal childhood, left school at age 14 yrs with no qualifications. Worked as a repairer of televisions and then as a driver. His wife described him as introspective and irritable. However, at age 39 yrs she noticed deterioration in his intelligence and social behaviour and he became increasingly lethargic He was unable to cope as a driver and worked as a part-time cleaner. He was admitted at age 41 yrs for investigation On examination he was disorientated in time and place, was unable to perform simple calculations or name the Queen. Muscle tone was symmetrically increased and upper limb reflexes were brisk and equal Plantar responses were flexor. There was no nystagmus, ataxia or sensory abnormality. Electroencephalography showed a low voltage record with marked slowing A CT scan demonstrated definite cortical atrophy. Psychometric assessment indicated a premorbid IQ of 94 on the Schonell word recognition test with grossly impaired cognitive function on the WAIS (verbal IQ 69, performance IQ 46, full-scale IQ 57). He refused to cooperate with memory testing. He progressively deteriorated and on examination at age 45 yrs his speech consisted of mumbling short sentences. He had increased tone of all limbs with shaking movements of the upper limbs. He was doubly incontinent At age 46 yrs he was taken into residential care and required sedation for aggressive and sexually disinhibited behaviour. He died at age 48 yrs. No autopsy was performed.

Case VI.17. Female, born 1944 No further information.

Case VI.18. Male, born 1940. Described by relatives as having always been short tempered. He was aggressive as a child and was expelled from school at age 14 yrs when several girls became pregnant. His family noticed that he was becoming forgetful at age 43 yrs. Around this time he was involved in a road traffic accident which involved a brief loss of consciousness. His memory deficit progressed and his handwriting deteriorated. By age 46 yrs he was unable to cope with his work as a diesel fitter On assessment at age 47 yrs his verbal IQ was estimated at 74 and performance IQ as 76. His estimated optimal IQ was 94. Memory for visual material was weak Nominal skills were satisfactory and spontaneous speech was fluent. Performance on perceptual tasks was poor and there was slowness on speed tasks. On examination there was increased tone in the legs of the Gegenhalten type but neurological examination was otherwise normal. Routine biochemical, haematological, endocrine and immunological screening was normal Examination of the CSF was normal. Neuro-opthalmologic examination was normal.

A repeat neuropsychology assessment at age 49 yrs showed no significant further deterioration with the exception of mild deterioration of non-verbal reasoning, visual memory and handwriting P300 measurements showed recorded potentials of normal latency for both auditory and visual tasks; however, the P300 amplitude recorded from central areas in the visual modality was bilaterally reduced. Positron emission tomography demonstrated cerebellar hypometabolism.

On reassessment at age 50 yrs there had been little further deterioration. He had developed bilateral pout reflexes Glabellar tap was positive There was a coarse tremor of hands present at rest. There was no ataxia, although he had difficulty with rapid alternating movements due to apraxia.

Case VI.19 Female, born 1942. Well.

Case VI 20. Male, born 1944. Normal childhood Left school at age 17 yrs and later became a company director. His wife described his normal personality as self-centred, argumentative and aggressive On one occasion at age 31 yrs he had beaten her badly. At age 34 yrs his wife noticed that he was becoming increasingly vague, forgetful and clumsy. This progressively worsened over the next few years and he began to get lost near home. At age 39 yrs he was feeling depressed and anxious with his lack of concentration and memory deficit and his GP prescribed amitriptyline. Following an argument with his wife after an episode of clumsiness he left home and took an amitriptyline overdose. A suicide note said that he felt that he was developing the same illness as his mother. He was admitted unconscious to an intensive care unit but made a full recovery. Neurological examination at this time was normal. Psychometric assessment showed slight memory impairment and evidence of good average premorbid intelligence. He was not felt to be demented or clumsy on observation on the ward and he was discharged to outpatient follow-up. Shortly after this admission he separated from his wife and declined further follow-up and EEG. He was seen again at age 42 yrs, as his second wife had noticed a marked deterioration over the preceding 6 mths He had been unable to keep a job over the past 3 yrs and was becoming aggressive His main problem appeared to be slowness rather than memory. He was noted to be dysarthric CT scan showed generalized moderate cerebral atrophy and a diagnosis of familial Alzheimer's disease was made. Repeat psychometric assessment showed marked deterioration in the Memory for Designs Test although little change on other tests. Over the next year he continued to deteriorate and at age 43 yrs he committed suicide by taking an imipramine overdose At autopsy the brain weighted 1392 g and showed no macroscopic abnormality No histological examination was performed.

Case VI.21. Male, born 1940. He had been unable to cope with his job as a lorry driver and gave this up 2 yrs prior to presentation (at age 42 yrs). He had developed increasing clumsiness and was unable to tie shoelaces. For the preceding 18 mths he had become increasingly obstinate and belligerant and his second marriage had broken up. Memory and concentration had also deteriorated. He was noted to have an unsteady gait the year before presentation. On examination he had a marked impairment of memory and intellectual function. His behaviour was inappropriate and he had no insight into his illness He had mild choreiform movements but no gait abnormality. Neurological examination was otherwise normal Verbal IQ was 60, performance IQ 63 and full-scale IQ 59. A CT scan showed cortical atrophy with normal caudate nuclei. Electroencephalography showed generalized non-specific abnormality

On review 9 mths later, he had developed leg cramps and was occasionally incontinent. Memory and behavioural problems had deteriorated further. He had become increasingly unsteady with frequent falls He was dysphasic. He was admitted to hospital 18 mths later having become unable to dress or wash himself. He was grossly demented and apraxic with blepharoclonus. Multifocal myoclonus was present mildly at rest and exacerbated by active or passive movement. He was unable to protrude his tongue Tendon reflexes were intact and plantar responses flexor He was uncooperative and aggressive and required sedation His condition deteriorated rapidly and he died age 45 yrs. Neuropathological findings are discussed above.

Cases VI.22–24. Males, born 1939–1945 Well.

Case VI.25. Female, born 1946. Presented at age 37 yrs with a 4-yr history of progressive intellectual deterioration. She had become unable to take simple decisions or write and lacked insight into her illness. On examination she had a mild dysarthria and expressive dysphasia. There was marked dyscalculia and severe impairment of short-term memory. There was a dressing apraxia and constructional apraxia. She was unable to follow complex commands. She had a flat affect and was unconcerned by her inability to perform simple tasks. Limb tone and power were normal Tendon reflexes were normal and plantar responses flexor. No choreiform movements were observed. Sensory examination was normal Gait was normal and coordination grossly intact. Electroencephalography demonstrated a slow dominant rhythm with minor excess of theta activity but no specific abnormality. Visual evoked potentials were normal A CT scan showed generalized atrophy.

On review 2 mths later involuntary movements were noted The diagnosis was felt to be Huntington's disease. At age 45 yrs she was unable to speak or understand speech. She could not hold a spoon or cup, and could only walk supported by two nurses. She was incontinent of urine and faeces. On examination involuntary movements were noted. There was frequent facial grimacing, jerking of the head, and a tendency to bring both hands up to the face. Myoclonic jerks were present. There was a general increase in tone in the limbs with brisk reflexes. Plantar responses were extensor

Case VI.26. Female, born 1927. Normal childhood, low educational achievement but was able to read and spell well Promiscuous since age 14 yrs, causing considerable concern to her father and stepmother and had two illegitimate children by different fathers Described as being of very pleasant personality but with a short temper if provoked. Always untidy, with poor personal hygiene; her family tended to treat her as a child. Had worked as a factory worker and printer until age 24 yrs. Involved in a road traffic accident at age 32 yrs at which she sustained a head injury and was hospitalized for several days Relatives stated that she showed more marked intellectual decline after this. From the age of 35 yrs she was unable to cook, wash or dress herself properly She was admitted to a psychiatric hospital then. Her writing had become illegible and she had difficulty finding words On examination there was severe memory impairment and dyscalculia. Tone and power in the limbs was normal and tendon reflexes were symmetrically brisk with flexor plantar responses. No abnormal movements were noted. Wassermann reaction was negative Electroencephalography showed atypical spike and wave activity. Air encephalography was normal. Neuropsychological testing showed gross impairment on performance tests but relative preservation of verbal functions. A diagnosis of presenile dementia was made. She was readmitted at age 38 yrs when her father and stepmother were unable to cope with her at home. There was a marked deterioration of intellectual function with severe expressive and moderate receptive aphasia She had difficulty walking On examination she was additionally noted to be dysarthric and to have a tremor of the tongue. At age 40 yrs she was noted to be ataxic and to have an extensor plantar response on one side The diagnosis was considered to be Pick's disease. At age 41 yrs she was noted to have athetoid movements. She had spasticity and developed contractures She had numerous bedsores. She died age 41 yrs with bronchopneumonia.

Case VI.27. Male, born 1930 Well

Case VI.28. Female, born 1932 Known to be demented from case notes of affected relatives. Died age 42 yrs in a psychiatric hospital. Cause of death 'marasmus and traumatic dementia and epilepsy'

Cases VI.29–30. Males, born 1932 and 1935. No further information.

Case VII.1. Male, born 1940 Died age 44 yrs of heart disease.

Case VII.2. Female, born 1945. Presented in 1983 with a 3- to 4-yr history of falls related to myoclonic jerking Electroencephalography showed bilateral atypical spike-wave activity, and a diagnosis of myoclonic epilepsy was made.

She was treated with clonazepam On review in 1986 she was having frequent falls and was afraid to go out There had been a change of personality with progressive apathy, loss of activity and memory impairment. She had attacked her husband but was not normally aggressive. She was disorientated in time and unable to perform simple sums General knowledge and comprehension were poor There was marked left/right disorientation and she could not follow instructions to lie on her back Plantar responses were flexor Fundi were normal Her gait was waddling on a wide base and she held her left arm to the side Investigation showed a slightly raised γ glutaryl transferase. The EEG now showed an excess of slow wave activity with some localized sharp waves in the left hemisphere. Examination of CSF was normal. A CT scan showed very severe diffuse atrophy. On review 2 mths later she was dysarthric and unable to stand unaided or walk without support. She died age 43 yrs from bronchopneumonia. The neuropathological findings are discussed above

Case VII.3 Female, born 1937. Presented in 1978 with a 6-mth history of headaches, slurring of speech and difficulty with arithmetic Her premorbid personality and intellect were apparently normal On examination she had a severe global dysphasia and mild dysarthria There was a dressing apraxia and a marked deficit of short-term memory. She was unable to remember the names of her children and was disorientated to place and time Neurological examination was otherwise normal with symmetrical reflexes and flexor plantars A CT scan showed generalized cortical atrophy A diagnosis of Alzheimer's disease was made She was reassessed in 1982 when she had become emotionally labile and difficult to manage at home She had become unsteady while walking with occasional falls, was unable to wash herself and had become incontinent of urine. There was a marked increase in appetite with gross obesity. On examination tone and power in the limbs were normal. Reflexes were symmetrical with flexor plantar responses. There were bilateral grasp reflexes No involuntary movements were noted The gait was wide based. On investigation alkaline phosphatase was elevated, other liver function tests were normal. Examination of the CSF was normal. A CT scan showed progressive cerebral atrophy. The diagnosis, in view of the family history, was thought to be Huntington's disease. Several months later she was admitted for long-term care

On reassessment in 1987 she was severely demented and aphasic She was sexually disinhibited. No chorea was seen but myoclonic jerks were observed There was extrapyramidal rigidity. She had been treated with thioridazine Reflexes were symmetrical and brisk with flexor plantars. By 1989 she was bedbound and required total nursing care. She died at age 53 yrs from bronchopneumonia. Neuropathological examination is in progress

Case VII.4 Female, born 1940 Presented at age 48 yrs with history of gradual deterioration of performance at work having been unable to cope at all at work for the previous year. She denied any difficulty. On examination she was orientated to time and place but with a marked memory impairment and dyscalculia. Neurological examination was otherwise normal with no primitive reflexes or abnormal movements. There has been slow deterioration of cognitive function since this assessment

Case VII.5 Female, born 1941. Presented 1981 with a several-year history of progressive dementia Diagnosis was of Huntington's disease Died age 45 yrs, cause of death 'bronchopneumonia and Huntington's disease'

Case VII.6 Male, born 1954. Well.

Case VII.7. Female, born 1957. Adopted as an infant and well until age 23 yrs when she was noted to have poor concentration and excessive mood swings. She had to give up her job 2 yrs later because of difficulty with calculation. Over the following year she became unable to dress or go shopping and her writing became illegible. On admission to hospital at age 29 yrs she denied neurological symptoms and was emotionally labile. She had marked dyscalculia, dysgraphia, dyslexia and an expressive dysphasia. She could not copy a circle and had a dressing apraxia. She was aware of recent events and had good recall for past events. Tone, power and coordination were normal in the limbs with pathological brisk tendon reflexes but flexor plantar responses. The gait was slightly broad based.

On investigation, haematological, biochemical and endocrinological tests were normal, as were examination of the CSF, evoked potentials, nerve conduction studies and lysosomal enzymes. Computerized tomography and MRI showed cerebral and cerebellar atrophy (Fig 9). Electroencephalography showed infrequent brief generalized epileptiform discharges. She had verbal and performance IQs of 78 and 64, respectively, with multiple cognitive deficits as described above but with relative sparing of verbal and visual memory. Further deterioration has occurred over the past 4 yrs but she is still able to carry out a limited conversation. She has developed stimulus sensitive (to stretch) myoclonic jerks in the arms. The initial clinical diagnosis was familial Alzheimer's disease

Case VII.8. Female, born 1957. Progressive intellectual deterioration from age 22 yrs. She became slow and apathetic and could not shop, cook or look after her family On admission to hospital at age 27 yrs she had had an unsteady gait for 2 yrs On examination she was grossly demented and had a mildly ataxic gait, slight postural tremor, brisk reflexes and extensor plantar responses A CT scan showed mild cerebral atrophy. She had a verbal IQ of 63 and a performance IQ of 48 There was global cognitive impairment with evidence of dysphasic and perceptual deficits; memory function was severely impaired On reassessment 7 yrs later she was severely globally demented and had a shuffling gait. There were occasional spontaneous axial myoclonic jerks

Case VII.9. Male, born 1959 Well.

Case VII 10. Female, born 1948. No further information.

Cases VII.11–13. Males, born 1951–1958. No further information

Case VII 14 Female, born 1948 Well until age 32 yrs when her husband noticed a gradual change in behaviour, she stopped doing the housework and cooking and became increasingly possessive and also depressed By age 37 yrs she became emotionally labile with aggression towards her husband. On assessment at age 40 yrs she was unable to walk far, tending to lean to one side and her speech had become slower with difficulty finding words Her husband had to help her eat, dress and bathe and there had been marked weight gain. On examination her speech was slow She scored nine out of 30 on the Mini Mental State examination She had marked memory impairment and was apraxic There was no evidence of dysphasia and verbal fluency was normal Snout reflex was present Tendon reflexes were brisk and symmetrical with flexor plantar reponses. Routine haematological, biochemical and endocrinological investigations were normal. Electroencephalography showed moderate diffuse and generalized slow wave disturbance A CT scan showed gross cortical atrophy

Case VII.15. Male, born 1952. Reported to have dementing illness. No further information available.

Cases VII.16–46. Born 1955–1971. No further information.

Case VII.47. Female, born 1963. Admitted to hospital at age 25 yrs She had had episodic disturbances of conciousness from about age 7 yrs until age 23 yrs Shortly before admission to hospital she had had a generalized seizure and for 2 yrs had noticed a gradual deterioration of her memory. On examination she was vague and unconcerned about her illness. Her attention was limited and short-term memory was poor. Language functions were intact but there was dyscalculia. Physical examination was unremarkable except from occasional brief muscle twitches of the outstretched hands Detailed psychological assessment showed a verbal IQ of 79 and a performance IQ of 77 Electroencephalography showed slight generalized slowing but no other abnormalities and a CT scan showed mild generalized cerebral and cerebellar atrophy.

Cases VII 48–61. Born 1962–1971. No further information.

Case VII.62. Male, born 1949. He was brought up by his maternal step-grandmother as both his mother and maternal grandmother had died with a presenile dementia He had a poor school record. He went to approved schools and prison for various offences At age 35 yrs he developed difficulty with attention and concentration, and apathy He was unable to complete tasks, especially those requiring visuospatial skills. In addition, he complained of unsteadiness in walking. At age 38 yrs there was noticeable memory loss. Following the death of his grandmother there was marked deterioration and he exhibited inappropriate behaviour with episodes of violence and increasing difficulty finding words. On examination at age 38 yrs his score on the Mini Mental State examination was 20 out of 30 but motor examination including gait was normal. Speech was normal Routine biochemical and haematological testing was normal Electroencephalography was normal. A CT scan demonstrated cerebral atrophy. He became unable to cope with his work and lost his job. At age 39 yrs there had been further deterioration with a Mini Mental score of 19 out of 30, dyscalculia, constructional dyspraxia and mild expressive dysphasia with impaired verbal fluency. His mood was inappropriate and labile with irritability and aggressive remarks. He had difficulty learning new material but recent and remote memory was only moderately impaired. He had a marked attention defect His abstract thinking was relatively intact He had a snout reflex and hypertonicity with opposition to passive movement and inability to relax. Tendon reflexes were symmetrical and plantar responses flexor. Coordination was impaired. His gait was mildly ataxic. Psychological testing revealed a verbal IQ of 70, a performance IQ of 76 and a full-scale IQ of 71 Estimates of his premorbid IQ were verbal 84, performance 95 and full scale 91. A CT scan showed generalized miled cerebral atrophy The diagnosis was of familial Alzheimer's disease and he was enrolled in a clinical trial of tetrahydroaminoacridine.

Case VII.63 Male, born 1952. He grew up in the care of his maternal step-grandmother He exhibited several antisocial personality traits during childhood including theft, fighting and being verbally abusive. He left school at age 17 yrs with no qualifications. His IQ was later assessed to be 100. He was referred to a psychiatrist at age 19 yrs with respect to his antisocial behaviour. At this stage he was working as an unskilled labourer. By age 21 yrs he was married with one son. He became increasingly aggressive from his early 20s, in particular toward his wife His loss of control was exacerbated by failure at simple tasks. He was convicted for attempted burglary and began to steal money openly. At this time he complained of loss of balance and was noted to have an intermittently unsteady gait. Two to three years later he became dysarthric with jerky abrupt speech. On assessment at age 27 yrs he showed obvious intellectual decline with memory loss and profound dyspraxia which resulted in complete dependency. The working diagnosis at this stage was presenile dementia. Diagnoses of Alzheimer's disease and Huntington's disease had been considered previously. He underwent formal assessment at age 30 yrs at which time he had negligible abilities on verbal tasks and had a severe memory deficit. He perseverated in verbal responses. In addition, he was severely ataxic and began to develop clonic episodes. Later he developed generalized seizures. he became rigid and anarthric in his last months and died at age 36 yrs with bronchopneumonia. Neuropathological findings are discussed above.

Cases VII.64–70, born 1956–1959 No further information

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VISUOSPATIAL ATTENTION IN DEMENTIA OF THE ALZHEIMER TYPE

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SUMMARY

Cue-directed shifts of spatial attention were examined for a letter-discrimination task in 15 patients with mild to moderate dementia of the Alzheimer type (DAT) and 15 healthy, age-matched controls. Spatial cues were valid, invalid or neutral in indicating probable target location and were presented either centrally at fixation or peripherally 6.7° to the left or right of fixation. Stimulus-onset asynchrony (SOA) between cue and target was varied between 200 ms and 2000 ms. Reaction time (RT) benefits conferred by valid cues did not differ between the DAT group and the controls. However, RT costs incurred by invalid cues were significantly greater in the DAT group than in the control group. Group differences in RT costs plus benefits occurred at short SOAs (<500 ms) for peripheral cues and at long SOAs (>500 ms) for central cues. Reaction time costs plus benefits were correlated with right-left asymmetry in resting levels of cerebral glucose metabolism in the superior parietal lobe for DAT patients but not for controls. The results indicate that focusing of attention to spatial location is intact in early DAT, whereas the disengagement of visuospatial attention is impaired. Automatic attention shifts elicited by peripheral cues reveal abnormalities earlier than attention shifts initiated 'effortfully' by central cues. Intact focusing and impaired disengagement of visuospatial attention may be linked to dysfunction in early DAT of cortico-cortical networks linking the posterior parietal and frontal lobes.

INTRODUCTION

There has been little formal study of attentional functioning in persons with dementia of the Alzheimer type (DAT), despite the recognition that attention deficits may constitute a significant aspect of the cognitive impairment in this disease (Jorm, 1986; Parasuraman and Nestor, 1986, 1991; Broks *et al.*, 1988; Nebes and Brady, 1989). The relative neglect of attention is surprising for at least three reasons. First clinical observations have long pointed, albeit in a general way, to the moderating influence of attention on the neuropsychological test performance of patients with dementia (Lezak, 1983). Secondly, there is an extensive literature indicating that attentional processes are affected by normal adult aging (Craik and Byrd, 1982; Plude and Hoyer, 1985; Salthouse, 1988). Given the overlap in cognitive functioning between normal aging and the very early, mild stages of DAT (Corkin *et al.*, 1984; McKhann *et al.*, 1984; Rubin *et al.*, 1989; Storandt and Hill, 1989), it would be important to know if the effects on attention of aging and dementia differ, and if so, whether quantitatively or qualitatively. Thirdly, many of the neural

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systems that are most affected by the Alzheimer's disease process may play significant roles in various attentional functions. The cell groups most damaged by Alzheimer's disease are the large pyramidal cells whose axons form connections between neocortical association areas (Pearson *et al.*, 1985; Morrison *et al.*, 1987, 1990) and cells in subcortical structures such as the cholinergic basal forebrain (Whitehouse *et al.*, 1982; Arendt *et al.*, 1985), the locus coeruleus (Bondareff *et al.*, 1982; Marcyniuk *et al.*, 1986) and the dorsal raphe nucleus (Curcio and Kemper, 1984; Yamamoto and Hirano, 1985), whose axons form widely distributed projections to neocortex. Position emission tomography (PET) studies of regional cerebral metabolism in patients with DAT have demonstrated that the selective involvement of the association neocortices is evident in the very early stages of this illness (Haxby *et al.*, 1986; Grady *et al.*, 1988). Corticocortical connections between the association areas of the parietal and lateral frontal lobes and ascending pathways from the cholinergic basal forebrain, locus coeruleus and dorsal raphe nucleus have been postulated to control functions of focusing, shifting and maintenance of attention over time (Mesulam, 1981; Parasuraman, 1984; Robbins, 1984; Aston-Jones, 1985; Goldman-Rakic, 1988).

Attention and cognition in dementia

What role does attention play in DAT? Two general views have been proposed. One sees attention as an intrinsic property of mental operations in general; for example, memory search, retrieval or response selection, and postulates that the efficiency of cognitive operations is dependent upon the efficient allocation of attention to those operations (Nebes *et al.*, 1984; Ober *et al.*, 1985; Hartman, 1991; Nestor *et al.*, 1991*a*). Attention is viewed as a general 'processing resource' (Kahneman, 1973; Gopher, 1986) that may be diminished or less easily allocable in DAT. According to this view, a given mental operation such as memory search may operate in much the same way in demented persons as in normals but does so less efficiently (e.g. slower or less accurately) in DAT subjects because of a deficit in attention allocation. Evidence for an attention allocation deficit in DAT has been reported in recent studies that have used divided attention or dual-task procedures (Baddeley *et al.*, 1986; Grady *et al.*, 1989; Nestor, *et al.*, 1991*a*).

A somewhat different approach to attention focuses on the various attentional mechanisms that allow the human information-processing system to process multiple stimulus features and control response outputs in a coherent manner. Some of these mechanisms may be impaired in DAT (Parasuraman and Nestor, 1986, 1991; Nebes and Brady, 1989). The attentional mechanisms that may be important include (among others) stimulus selection (focusing), switching of attentional focus and maintenance of attentional focus over time (Parasuraman and Davies, 1984; Posner and Marin, 1985; Allport, 1989). If deficits in these attentional operations are found in DAT, the implications would be significant, because they clearly participate in many of the higher-level cognitive functions that are impaired in DAT. Identification of attentional mechanisms affected by DAT will also bear on the attention-as-resource view of the role of attention in DAT. That is, impairments attributed to general deficits in 'attention allocation' may be parsed into abnormalities in selection, attentional switching, maintenance of attention and so on, and to more elementary deficits by fine-grained decomposition of these mechanisms into their component operations.

Shifts of visuospatial attention

A number of attentional operations may be important for understanding the development of cognitive deficits in DAT. However, there is indirect evidence suggesting that the switching of attentional focus may be disproportionately impaired in DAT, particularly in the early, mild stages of dementia. Clinical neuropsychological tests that provide gross measures of the focusing and shifting of visual attention, such as the Trail Making (Part B) and Stroop tests, have recently been shown to be sensitive to the onset of mild dementia, preceding deficits in all other non-memory cognitive functions (Grady *et al.*, 1988; Haxby *et al.*, 1988, 1990). Both these tests require subjects to adopt a particular stimulus 'set' and then to switch that set from time to time. While these tests do not reveal which component operation underlying attentional shifting contributes to the poor test scores, they clearly indicate that performance on tasks in which subjects have to shift their attentional focus may be significantly affected in the early, mild stages of DAT.

The present study examined shifts of spatial attention in patients with DAT and in healthy, age-matched controls. Visuospatial selective attention has been particularly well investigated in normal subjects, and a number of competing theories have been developed (Posner, 1980; Duncan, 1981; Eriksen and Yeh, 1985; LaBerge, 1990). Three other factors also influenced this choice. First, although the neural systems controlling attention are not very well specified, much of what is known concerns visuospatial attention [*see* LaBerge (1990) and Posner and Petersen (1990) for reviews]. A large body of evidence indicates that the posterior parietal lobe and portions of the frontal lobes form a distributed neural network (including the thalamus and other subcortical areas as well) that participates in the control of visuospatial attention (Mountcastle, 1978; Mesulam, 1981; Posner *et al.*, 1984*b*; Rizzolatti and Camarda, 1987; LaBerge, 1990). Secondly, PET studies of regional cerebral metabolic rates for glucose (rCMR-glc) indicate that this fronto-parietal system may be dysfunctional at an early stage in the development of Alzheimer's disease (Haxby *et al.*, 1986; Horwitz *et al.*, 1987; Grady *et al.*, 1988). Thirdly, rCMR-glc rates show increased hemispheric asymmetry for association areas of the parietal, temporal and frontal cortices, with the direction of lateral asymmetry determining the relative severity of deficits in language and visuospatial function: right hypometabolic patients exhibit visuospatial deficits and left hypometabolic patients language-related deficits (Haxby *et al.*, 1985). In very mildly demented patients, these metabolic asymmetries precede (and correctly predict) the subsequent appearance of visuospatial or language deficits (Haxby *et al.*, 1986, 1990). Given that deficits in the orienting of visuospatial attention have been attributed to right posterior parietal lobe dysfunction (Heilman and Van Den Abell, 1980; Mesulam, 1981; Weintraub and Mesulam, 1987), we reasoned that the efficiency of visuospatial attention shifts in patients with DAT would be related to right-left differences in glucose metabolic rates in the posterior parietal lobes.

Although visual information is usually selected by eye and head movements towards a spatial location, stimuli at a non-fixated location can be responded to without overt eye movements to that location. Such covert attention shifts enhance stimulus processing at attended locations compared with unattended locations (Eriksen and Hoffman, 1972; Posner, 1980). Spatial attention is manipulated by an advance cue that directs the subject's attention to a given location where the stimulus will occur. Many studies have shown that such precues: (i) reduce simple reaction time (RT) to a super-threshold stimulus presented at that location (Posner *et al.*, 1980); (ii) increase sensitivity to a threshold stimulus (Bashinski and Bacharach, 1980); (iii) reduce choice RT to stimuli that must be discriminated (Eriksen and Yeh, 1985; Lambert and Hockey, 1986); (iv) increase accuracy in discriminating between two stimulus forms (Müller and Findlay, 1988; Bahri and Parasuraman, 1989); (v) increase the amplitude of early-latency (i.e. sensory) brain potential components elicited by a stimulus at the attended location (Mangun *et al.*, 1987).

The evidence is thus compelling that advance cues, which direct a person's attention appropriately to a stimulus location, enhances sensory processing at that location, resulting in benefits in RT or accuracy (Hawkins *et al.*, 1990). In contrast to such valid location cues, invalid cues that incorrectly direct attention to another location result in costs in RT or accuracy, presumably because of the need to shift attention away from the incorrect to the correct location. The use of 'neutral' cues that provide no information on the location of the target allows benefits and costs to be assessed separately: RT benefit = neutral cue RT − valid cue RT; RT cost = invalid cue RT − neutral cue RT. Alternatively, total RT costs plus benefits can be computed as invalid cue RT − valid cue RT.

Posner *et al.* (1984*b*) suggested that at least three component processes underly attentional shifts in spatially cued tasks: engagement (or focusing), shifting (or movement) and disengagement (or reorienting) of attention. A cost-benefit analysis was used to show that valid cues are associated with a reduction or benefit in RT (relative to neutral trials), whereas invalid cues lead to an increase or cost in RT. Posner *et al.* (1984*b*) showed that posterior parietal lobe damage markedly affected attentional disengagement. Patients with unilateral parietal lobe lesions were slow to respond to a target contralateral to the lesioned hemisphere if attention was directed to the opposite location by an invalid cue. Subsequent studies have found that this deficit occurs when the direction of the attention shift is contralesional as opposed to ipsilesional, regardless of whether the shift is in the visual field contralateral or ipsilateral to the parietal lesion (Posner *et al.*, 1987; *see also* Làdavas, 1987, 1990; Reuter-Lorenz *et al.*, 1990).

Attention may be shifted to spatial locations by one of two controlling mechanisms: 'voluntary' shifts are initiated in response to symbolic cues, e.g. a central arrow pointing to the left or right; and 'obligatory' shifts initiated by highly salient cues near the expected stimulus location, e.g. a peripheral bar marker or the abrupt onset of a light in the periphery (Posner, 1980). Jonides (1981) showed that central and peripheral cues differ in fundamental ways in their effect on attentional shifting. Central cues are thought to require 'effortful' or 'controlled' processing because of their indirect, symbolic nature. Their dependence on effortful attention is demonstrated by the fact that central cue effects can be abolished by a concurrent memory load (Jonides, 1981) or by a secondary task (Posner *et al.*, 1984*a*). Peripheral cues, on the other hand, draw attention involuntarily and are not affected by memory load, thus qualifying to be characterized as automatic. Jonides and Yantis (1988) have linked the ability of peripheral cues to call attention automatically to the unique status of abrupt onsets in the peripheral visual field and to their effects on 'transient' (vs 'sustained') neural pathways in the visual system (Kulikowski and Tolhurst, 1973). Central and peripheral cue effects also differ in their time course (Posner, 1980; Jonides, 1981). The automatic attentional shifting process triggered by peripheral cues is fast acting, being most effective at short cue-target stimulus-onset asynchronies (SOAs). The more effortful process initiated by central cues, on the other hand, is primarily effective at longer SOAs (Müller and Rabbitt, 1989; Cheal and Lyon, 1992).

Two previous studies have briefly reported on spatial shifts of visual attention in DAT (Nissen *et al.*, 1981; Freed *et al.*, 1989). Both studies used the same simple RT task requiring detection of a single letter presented to the left or right of fixation, and preceded by a central arrow cue at very long cue-target SOAs (2000 ms and 3000 ms). Nissen *et al.* (1981) reported that DAT subjects had the same cue validity effects as controls at a 2000 ms SOA but showed no cue effects at a 3000 ms SOA, whereas Freed *et al.* (1989) did not report DAT-control differences in cue effects at either SOA. Cue effects on attentional selectivity are usually found at much shorter intervals, in the range 150–500 ms, in both normal young (Posner, 1980) and older adults (Greenwood *et al.*, 1989; Madden, 1990), and there are also important differences in the time course of these effects with different cue types (Müller and Rabbitt, 1989). In the present study we therefore examined visuospatial attention shifts for central and peripheral cues presented at shorter SOAs (200 ms and 500 ms). We also used a letter-discrimination task rather than a simple letter-detection task so as to investigate the effects of visuospatial attention at a higher level (e.g. discrimination or identification) than simple luminance or energy detection. However, we also used a 2000 ms SOA and a letter-detection task in some conditions for the sake of comparison with the previous study by Nissen *et al.* (1981).

Hypotheses and predictions

Cue-directed shifts of spatial attention in patients with DAT and age-matched controls were investigated. We had three major hypotheses. First, DAT subjects should show a selective impairment relative to age-matched controls in the effects of spatial cueing in a letter-discrimination task. Given that the posterior parietal lobe is dysfunctional in DAT, we predicted that the impairment would be specific to the effect of invalid cues, namely that the RT costs due to shifts of attention away from an incorrect location would be greater in DAT subjects, whereas RT benefits due to valid cues would be normal.

Secondly, we hypothesized that RT costs plus benefits would vary with cue type (central or peripheral) and cue-target SOA. The rationale was the finding that peripheral cues are fast acting and initiate attentional shifts automatically, whereas central cue effects are slower and require effortful processing (Jonides, 1981; Müller and Rabbitt, 1989). Subjects with DAT should show greater RT costs plus benefits with both central and peripheral cues. However, because the time course of cue-initiated attentional effects differ for central and peripheral cues, we reasoned that differences in RT benefits and costs between DAT subjects and controls would vary with SOA. Specifically, we predicted that for peripheral cues, DAT subjects would show greater RT costs plus benefits (relative to controls) primarily at shorter cue-target SOAs, the time period where peripheral cues have their greatest impact (Müller and Rabbitt, 1989). On the other hand, for central cues, group differences in RT costs plus benefits should occur mainly at longer SOAs.

Thirdly, we hypothesized that the above pattern of RT costs plus benefits, if found, would be linked to resting levels of cerebral glucose metabolism in the right and left superior parietal lobes. Lesions of the parietal lobe lead to impairments in disengaging spatial attention, with greater impairments for right-hemisphere lesions (Posner *et al.*, 1984*b*; Baynes *et al.*, 1986; Petersen *et al.*, 1989). Neglect of contralateral hemispace is typically more common and pronounced when the right rather than the left hemisphere contains lesions (Critchley, 1953; Mesulam, 1981; Weintraub and Mesulam, 1987). This has been attributed to dysfunction of the normal bilateral control of visuospatial attention by the right hemisphere (Heilman and Van Den Abell, 1980). An alternative view attributes left-sided neglect to a diminished right-hemisphere bias for orienting attention contralaterally (Kinsbourne, 1987; Làdavas, 1987; Reuter-Lorenz *et al.*, 1990). Either view would predict that DAT subjects with relatively less metabolic activity in the right superior parietal lobe (compared with the left) would show increased RT costs plus benefits compared with those subjects who had relatively more metabolic activity in the left parietal lobe (compared with the right). Moreover, Posner *et al.* (1984*b*) found that parietal-lesioned patients showed increased costs of disengaging attention in response to an invalid cue for targets presented contralateral to the lesion. We therefore investigated whether metabolic asymmetry in the superior parietal lobe was similarly associated with visual-field asymmetry in the disengagement of attention by DAT patients.

METHODS

Subjects

Two groups of 15 subjects were tested, an early DAT (mild to moderately demented) group and a group of matched controls (normal older persons screened for health status). The DAT group consisted of 15 right-handed patients (11 males, four females) with a mean age of 71.8 yrs meeting the NINCDS–ADRDA diagnostic criteria (McKhann *et al.*, 1984) for 'probable' Alzheimer's disease. Patients with DAT were either referred by their physicians or were contacted independently. Subjects with DAT had no focal brain abnormalities as revealed by CT scan, had scores of less than four on the Hachinski Ischemia Scale (Hachinski *et al.*, 1975) and had no other current disease that could compromise brain function. A number of other procedures, including neurological examination, neuropsychological tests, psychiatric interview, physical examination and blood chemistry profile, were carried out to screen out individuals with dementia due to other causes. Although diagnosis of DAT according to these criteria is tentative, autopsy (Sulkava *et al.*, 1983) and biopsy (Neary *et al.*, 1986) studies indicate that histopathological confirmation of the clinical diagnosis of DAT occurs in about 80% of cases with these procedures. These rates can be increased further with serial neuropsychological testing (Huff *et al.*, 1987; Martin *et al.*, 1987). All patients in this study were participants in an ongoing longitudinal study of early DAT. (For representative results on serial neuropsychological tests in these patients, *see* Haxby *et al.*, 1990.) The DAT group had mean Mini-Mental Scale (MMS) and Mattis Dementia Scale (MDS) scores of 21.3 and 116.5, respectively, and a mean full-scale WAIS IQ of 106 (*see* Table 1). The majority of the DAT patients (12 subjects) had mild deficits (MMS 20–28, MDS 115–132), with three subjects being moderately demented (MMS 13–17, MDS 86–96).

The matched control group consisted of volunteers recruited through advertisements and selected on the basis of health status. This group comprised 15 normal adults (nine males, six females) with a mean of 70.7 yrs matched for age and years of education with the early DAT group. All but one of the controls were right-handed. Twelve of the 15 control subjects underwent the same screening procedures as the DAT group. Three control subjects were not screened rigorously but reported themselves to be in good health with no health problems within the last 5 yrs. Individuals with major psychiatric, neurological or cardiovascular disease, alcoholism or drug abuse were excluded. Control subjects did not differ significantly from DAT subjects in age or education level, but did do so on the MMS, MDS, WAIS IQ, Porteus Maze, Trails Part B and Stroop tests (*see* Table 1).

All procedures were approved by institutional review and informed consent was obtained from all patients and control subjects.

Visuospatial attention shifting task

A letter-discrimination task modelled after the covert visual attention paradigm developed by Posner (1980) was used. On each trial a warning 'plus' sign appeared for 1 s at the centre of a computer monitor. The warning signal was replaced by a location cue which remained on for a variable interval before the

TABLE I DEMOGRAPHIC CHARACTERISTICS AND NEUROPSYCHOLOGICAL TEST SCORES FOR PATIENTS WITH DEMENTIA OF THE ALZHEIMER TYPE (DAT) AND AGE-MATCHED CONTROLS

	DAT *Mean (SE)*	*Controls* *Mean (SE)*
Number	15	15
Age	71.8 (2.4)	70.7 (2.2)
Education (years)	14.4 (0.9)	16.3 (0.6)
Gender	11 F, 4 M	9 F, 6 M
Mini-Mental Scale*	21.3 (1.1)	29.8 (0.1)
Mattis Dementia Scale*	116.5 (3.8)	138.9 (1.4)
WAIS IQ*	105.7 (3.1)	131.7 (2.9)
Porteus-Maze Test (test age, years)*	12.1 (1.1)	15.2 (0.5)
Trail Making Test, Part B (seconds)*	304.1 (40.6)	80.1 (7.9)
Stroop Test*	15.5 (2.5)	32.7 (2.7)

*Difference between DAT patients and controls significant by t test, $P < 0.05$

target stimulus was presented. The cue-target SOA was varied within a block of trials between 200 ms, 500 ms and 2000 ms. Cues were valid, invalid or neutral in indicating probable target location. On valid and invalid cue trials, the cue was either a left- or right-pointing arrow that indicated the probable location of the subsequent target stimulus. On neutral trials the cue was an asterisk. Cue validity was varied within a block of trials. Cues were valid on 62.5%, invalid on 18.75% and neutral on 18.75% of the trials within a block (i.e. cue validity was 77% when a directional cue was presented). Valid and invalid cues were presented at one of two locations, central or peripheral. In the central condition the arrow cues were presented at the centre of the monitor; in the peripheral condition they were presented 6.7° to left or right of centre. Cue type was varied between blocks of trials. On each trial the cue was followed (after a variable SOA) by a target letter presented either 6.7° to the left or to the right of centre. The target remained on until responded to or until 2 s had elapsed, whichever came first. The subject's task was to maintain fixation at the centre of the monitor throughout the trial and to depress one of two response buttons (with the index finger of the left or right hand) according to whether the target letter was a vowel (A, E or U) or a consonant (B, D, F, H, L, P, R, S or T). The appropriate hand for responding to vowel and consonant targets (which were equiprobable) was randomized between subjects. Subjects were instructed to respond as quickly as possible within a maximum response window of 2000 ms. After a variable interval (between target onset and the start of the next trial) of 2200 ms, 2500 ms or 2800 ms, the next trial was presented.

Subjects were administered the RT tasks in the following order. (i) One block of 50 trials of simple RT, in which the central fixation stimulus (plus sign) was followed after a randomized interval (around a mean of 1 s) by the letter X, presented centrally. Subjects were instructed to respond as quickly as possible within a maximum response window of 1 s. (ii) A practice block of 20 trials was followed by four test blocks of 96 trials each of the letter-discrimination task, two with central cues and two with peripheral cues. The order of presentation of the central and peripheral cue location conditions was randomized. (iii) Two blocks of 96 simple letter-detection trials presented as a target letter the single letter X, to which subjects were required to respond by depressing a response button held in the right hand. Cues were presented at the central location only. All other aspects of the task were the same as for the letter-discrimination task. (iv) The simple RT task was administered a second time in order to assess the possible contribution of differential effects of fatigue to group differences in performance.

Measurement of resting regional cerebral metabolism

Regional cerebral metabolic rates for glucose were obtained in the resting state (eyes covered, ears plugged) using PET and [^{18}F]2-fluoro-2-deoxy-D-glucose (^{18}FDG). Positron emission tomography scans taken close to the times when the attention shifting task was administered were available for 14 of the 15 DAT subjects and 11 of the 15 controls. Positron emission tomography scans were performed on a Scanditronix PC1024-7B tomograph (Uppsala, Sweden), a seven-slice machine with a traverse resolution of 6 mm and an axial resolution of 10 mm. Transmission scans were used to calculate an empirically defined attenuation coefficient.

^{18}FDG (5 mG) was injected i.v. and arterial blood was sampled periodically during the uptake period and the scan to provide plasma for the measurement of radioactivity and glucose. Two scans of seven planes were obtained parallel to and 10–100 mm above the inferior orbitomeatal line, resulting in 14 interleaved planes. Anatomical areas were identified by comparing the PET images to a standard atlas (Eycleshymer and Shoemaker, 1911). [For additional details of the PET procedure, *see* Grady *et al.* (1990) or Kumar *et al.* (1991).] For this study, cerebral metabolic rates were calculated for four cortical regions. These were three areas thought to be part of the cortico-cortical network of visuospatial attention: superior parietal, inferior parietal and prefrontal cortex and, for control purposes, a cortical region not primarily involved in the shifting of visuospatial attention nor markedly affected by the Alzheimer's disease process, (lateral) occipital association cortex. For further definition of these regions, *see* Kumar *et al.* (1991). As described earlier, we predicted that right-left asymmetry in rCMR-glc in the superior parietal cortex would be related to the RT costs plus benefits of shifting visuospatial attention. We used the same procedure used by Haxby *et al.* (1985), who examined the relation between right-left metabolic asymmetries and performance on visuospatial and language tests. Haxby *et al.* (1985) found that absolute values of rCMR-glc were highly variable in both normal and demented subjects but that variability could be reduced by calculating asymmetry scores, thus increasing the likelihood of uncovering correlations between regional brain metabolic patterns and cognitive test performance. Right-left metabolic asymmetry indices (%) for each of the four cortical areas were calculated as follows:

$$\text{asymmetry index} = \frac{(\text{rCMR-glc})_{\text{right}} - (\text{rCMR-glc})_{\text{left}}}{\tfrac{1}{2}[(\text{rCMR-glc})_{\text{right}} + (\text{rCMR-glc})_{(\text{left})}]} \times 100$$

where $(\text{rCMR-glc})_{\text{left}}$ and $(\text{rCMR-glc})_{\text{left}}$ are the metabolic rates for homologous regions in the right and left hemispheres, respectively. A positive asymmetry index indicates greater right- than left-hemisphere metabolism (or relative left-hemisphere hypometabolism), a negative index greater left- than right-hemisphere metabolism (or relative right-hemisphere hypometabolism).

Data analyses

Mean accuracy scores for the letter-discrimination task (percentage correct) and median RTs for correct responses were computed for each cue validity condition (neutral, valid or invalid), cue type (central or peripheral), and SOA (200 ms, 500 ms or 2000 ms) Reaction times shorter than 100 ms were not included in the computation of median scores, and the upper limit for RT was 2000 ms. Both accuracy and RT were submitted to a 2×3×2×3 mixed-factorial analysis of variance (ANOVA) with a between-subjects factor of Group, and within-subjects factors of Cue Validity, Cue Type and SOA. Combined RT costs plus benefits associated with the cued trials were then computed (invalid cue RT – valid cue RT) and submitted to a 2×2×3 mixed-factorial ANOVA with a between-subjects factor of Group, and within-subjects factors of Cue Type and SOA. The neutral trial data were then used to compute separate benefit (neutral cue RT – valid cue RT) and cost (invalid cue RT – neutral cue RT) scores. The interpretation of RTs on neutral-cue trials is not straightforward because neutral cues differ physically from valid and invalid cues (asterisk vs arrows) and because attention may not always be focused at fixation on neutral trials (Jonides and Mack, 1984; Eriksen and Yeh, 1985). Nevertheless, the use of neutral cues does allow separate analysis of the costs and benefits of visual attention shifts in a simple manner. Hence it was felt worthwhile to carry out these analyses despite difficulties in interpretation because it was of interest to examine whether group differences in the effects of cues on RT reflected differences in RT benefits, RT costs or both. The detection-task accuracy and RT data were similarly analysed, except that because only central cues were used with this task, Cue Type was not a factor. Finally, the simple RT data were analysed in 2×2 ANOVA with factors of Group and Blocks (beginning and end of session).

RESULTS

Accuracy

ANOVA of the accuracy scores showed that the effect of Group was significant, F(1,28) = 6.79, $P < 0.05$. All other sources of variance (Cue Validity, Cue Type, SOA and their interactions) were not significant. Mean accuracy was 91.3% for the

DAT group and 99% for the control group. In general, both the DAT and the control subjects were highly accurate on the present letter-discrimination task, being able to maintain an error rate of less than 9%. Accuracy did not vary significantly with any condition.

Reaction time benefits and costs

Figure 1 gives the means of the median RTs for valid, invalid and neutral cues for both groups and for each cue type and SOA. The DAT subjects were significantly slower overall than the controls, $F(1,28) = 30.6$, $P < 0.0001$, and a significant effect for Cue Validity, $F(2,56) = 49.1$, $P < 0.0001$, indicated that the expected pattern of reduced RT for valid cues (benefit) and increased RT for invalid cues (cost), relative to neutral cues, was obtained. Significant effects due to Cue Type, $F(1,28) = 16.4$, $P < 0.001$, and Cue Type×Cue Validity×SOA, $F(4,112) = 7.9$, $P < 0.0001$, were also found, indicating that central and peripheral cues had differing effects on RT costs plus benefits depending on SOA. As is evident in Fig. 1, cue effects for central cues were stronger at the longer SOAs (500 ms and 2000 ms), whereas they were stronger for peripheral cues at the shortest SOA (200 ms) in patients with DAT and equally strong across all SOAs in controls. The magnitude of these cue effects varied between groups, particularly for invalid cues, as supported by the significant interactions of Group×Cue Type, $F(1,28) = 8.4$, $P < 0.01$, and Group×Cue Validity Cue Type×SOA, $F(4,112) = 2.7$, $P < 0.05$. All other sources of variance were not significant.

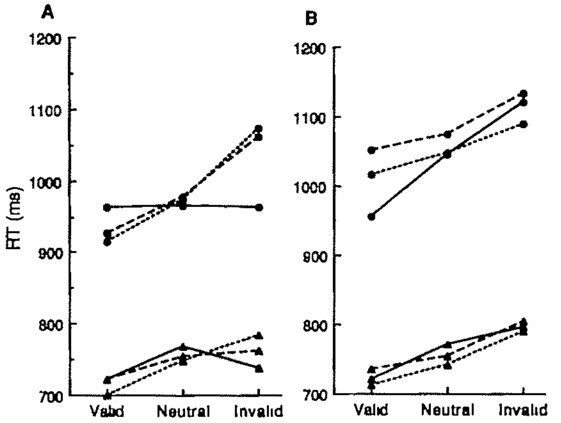

FIG 1. Mean reaction times (RTs) as a function of cue validity (valid, neutral, invalid) and stimulus-onset asynchrony (SOA: ——, 200 ms; —-, 500 ms; – – –, 2000 ms) for patients with dementia of the Alzheimer type (DAT) (●) and age-matched controls (▲). Data for central cues are plotted in panel A and for peripheral cues in panel B.

The four-way interaction between group, cue validity, cue type and SOA can be more easily understood by examining combined RT costs plus benefits (invalid RT−valid RT). Figure 2 shows the mean RT costs plus benefits for each group and condition. The DAT group had significantly higher overall RT costs plus benefits than controls, $F(1,28) = 4.4$, $P < 0.05$. However, this group difference interacted with Cue Type and SOA, $F(2,56) = 6.8$, $P < 0.003$. To probe the Group×Cue Type×SOA interaction further, the simple effects of Group were computed for each level of the Cue Type and SOA factors. For the central cues, the effect of Group was not significant for the

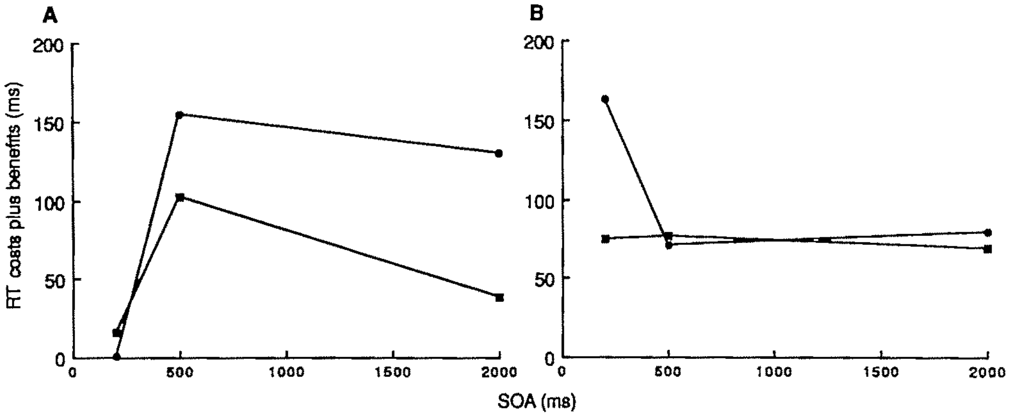

FIG. 2 Mean RT costs plus benefits (invalid cue RT − valid cue RT) as a function of SOA (200 ms, 500 ms or 2000 ms) for DAT patients (●) and controls (■). Data for central cues are plotted in panel A and for peripheral cues in panel B

200 ms SOA, F(1,68) < 1, and the 500 ms SOA, F(1,68) = 2.4, $P > 0.05$, but was significant for the 2000 ms, SOA F(1,68) = 7.4, $P < 0.01$. For the peripheral cues, the opposite pattern emerged; the effect of Group was significant for the 200 ms SOA, F(1,68) = 7.0, $P < 0.02$, but not for the 500 ms or 2000 ms SOAs, F(1,68) < 1. [Satterthwaite's procedure (*see* Winer, 1971, p. 530) was used in these tests of simple effects to correct the within-cell degrees-of-freedom, because the within-cell error term combines heterogenous sources of variance.] Figure 2 shows that RT costs plus benefits for central cues were greater for the DAT group at 2000 ms, also greater at 500 ms (but which proved not significant), and no greater at 200 ms. For peripheral cues, there was a clear group difference in RT costs plus benefits at 200 ms but not at 500 ms or 2000 ms. Thus, with central cues, the DAT patients showed greater RT costs plus benefits than controls (130 ms vs 39 ms) at long cue-target intervals (>500 ms). With peripheral cues, the DAT group showed greater RT costs plus benefits than controls (176 ms vs 75 ms) at short cue-target intervals (<500 ms).

To examine whether these group differences in cue validity effects were due to differences in RT benefits, costs or both benefits and costs, separate RT benefit and cost scores were analysed by subtracting neutral-trial RTs from cued-trial RTs. Figure 3 shows mean RT benefits and RT costs as a function of cue type and group. For RT benefit scores the only significant effect was the Cue Type×SOA interaction, F(2,56) = 3.9, $P < 0.03$. This interaction arose because for central cues RT benefits increased from 200 ms to 500 ms (being highest at 500 ms), whereas for peripheral cues RT benefits decreased with SOA (being highest at 200 ms). All other sources of variance, including Group, were not significant. Thus, the DAT and control groups did not differ significantly in overall RT benefits afforded by a valid cue, whether presented centrally or peripherally (*see* Fig. 3A). The mean RT benefit (across all conditions) was 43 ms for the DAT group and 39 ms for the control group. For RT costs, the effects of Group, F(1,28) = 4.24, $P < 0.05$ and the Cue Type×SOA interaction, F(2,56) = 3.62, $P < 0.05$, were significant. All other sources of variance were not significant. The significant effect for Group resulted from the higher RT costs

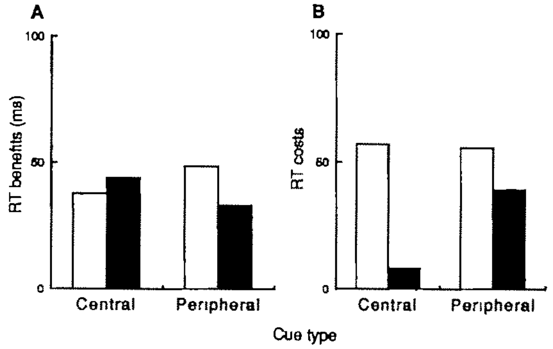

FIG 3. Mean RT benefits (panel A: neutral cue RT−valid cue RT) and costs (panel B: invalid cue RT−neutral cue RT) for DAT patients (open columns) and controls (filled columns) and for central and peripheral cues.

shown by the DAT group compared with the control group (*see* Fig. 3B). The mean RT cost (across all conditions) for control subjects was 24 ms; for DAT patients mean RT cost was 56 ms.

Three further aspects of the RT data should be noted. First, the Group×Cue Type ×SOA interaction was not significant in the separate costs and benefits analyses, whereas this interaction was significant in the combined costs plus benefits analysis. This indicates that the group differences in cue effects as a function of cue type and SOA found in the combined analysis cannot be reliably attributed to differences in benefits alone or costs alone. However, the fact that there was no overall significant group difference in RT benefits, whereas there was in RT costs, suggests that the results from the combined analysis are primarily due to group differences in RT costs. Secondly, RT costs and benefits were unrelated to individual differences in either intelligence ($r = -0.14$) or education ($r = -0.05$). Thirdly, the contribution of eye movements to group differences in RT benefits and costs was probably small. Eye movements were monitored for a subset of subjects in each group with the use of a simple mirror and camera arrangement. (The clinic setting in which testing was carried out precluded the use of more sophisticated techniques.) Subjects complied quite well with the instruction to maintain fixation in the central cue condition. Eye movements occurred on average on 1.6% of cued trials for the DAT group and on 0.1% of cued trials for the controls (500 ms and 2000 ms SOA only). Thus, it is unlikely that changes in RT due to attentional shifts were confounded with eye movements to cued locations. Eye movements were much more frequent in the peripheral cue condition, averaging 39.7% for the DAT group and 26.3% for the control group. Thus, eye movements could have contributed to RT differences associated with attention shifts in the peripheral cue condition. But significant group differences in RT costs plus benefits in this condition were found only at the 200 ms SOA, which was probably insufficient time for the DAT patients to move their eyes to the cued location. Furthermore, previous studies have found that RT benefits and costs can be dissociated from eye movements (Posner and Cohen, 1984; Shulman *et al.*, 1985).

Regional cerebral metabolic rates

Regional cerebral metabolic rates for glucose and right-left metabolic asymmetry indices were computed for both DAT and control subjects for the four cortical regions of interest. Table 2 gives the means and standard deviations of the asymmetry indices for patients

TABLE 2. RIGHT/LEFT ASYMMETRY INDICES (%) FOR rCMR-glc FOR PATIENTS WITH DAT AND AGE-MATCHED CONTROLS FOR FOUR CORTICAL REGIONS

	rCMR-glc asymmetry				*rCMR-glc/RT correlations*			
	DAT		*Controls*		*DAT*		*Controls*	
	Mean	*SD*	*Mean*	*SD*	*Central*	*Peripheral*	*Central*	*Peripheral*
Superior parietal	1.3	11.2*	1.6	5.5	−0.42	−0.54†	−0.14	0.06
Inferior parietal	7.7	16.5*	−1.1	6.4	−0.11	−0.05	0.11	−0.23
Prefrontal	4.7	6.8	−0.1	4.6	−0.26	−0.28	−0.36	0.21
Occipital	0.4	10.1	1.1	7.6	0.10	−0.08	−0.25	−0.23

A positive index indicates relative left-sided hypometabolism, a negative index relative right-sided hypometabolism. Correlations with RT costs plus benefits in the central and peripheral cue conditions are also shown. Negative correlations between rCMR-glc asymmetry and RT costs plus benefits were predicted for the DAT group. *Difference between DAT patients and controls significant by F test of equality of variance, $P < 0.01$. †Significantly different from 0, $P < 0.05$

and controls. While there were no significant differences between groups in mean asymmetry values for any of the four regions, the standard deviations in rCMR-glc asymmetry in the superior and inferior parietal association cortices were significantly greater in the DAT group than in the controls. Variability in metabolic asymmetry for the prefrontal and occipital regions was not significantly different between groups.

Product-moment correlations between metabolic asymmetry scores and the costs plus benefits of shifting of visual attention (invalid RT−valid RT) were computed for each of the four cortical regions and for both the DAT and control groups. We had predicted that: (i) group differences in RT costs plus benefits would vary with cue type and SOA, being greater for long SOAs with central cues and greater for short SOAs with peripheral cues; and (ii) that metabolic asymmetry in rCMR-glc in the superior parietal cortex would be correlated with RT costs plus benefits in DAT patients but not in controls. To restrict the number of possible correlations (and hence the risk of spurious associations), correlation coefficients were computed only for the four cortical regions of interest in the conditions in which significant group differences in RT costs plus benefits were obtained (central cues at 2000 ms, peripheral cues at 200 ms). Table 2 lists the correlations for both groups. With the small sample sizes due to the limited availability of PET data (14 DAT patients, 11 controls), the results are exploratory. Nevertheless, some interesting patterns emerged.

For the DAT group, a significant correlation of −0.54 was obtained between rCMR-glc asymmetry and RT costs plus benefits for the peripheral cue condition for the superior parietal area. Correlations were non-significant for the prefrontal, inferior parietal and occipital areas. For controls, the correlations were low and not significant for all four cortical regions. For the central cue condition, a similar pattern of a moderate correlation for the DAT group only was found for the superior parietal area (−0.42) and low correlations for other areas, but in this case none of the correlations was statistically significant.

As shown elsewhere, asymmetry is due to hypometabolism of the cortical region of interest, with the direction of asymmetry indicating whether the left or right hemisphere is more hypometabolic (Haxby *et al.*, 1990; Kumar *et al.*, 1991). The significant negative correlation for the DAT group for peripheral cues indicates that DAT subjects with lower right- than left-hemisphere metabolic rates (negative asymmetry index; relative right-hemisphere hypometabolism) had higher RT costs plus benefits than DAT subjects with lower left- than right-hemisphere metabolic rates (positive asymmetry, relative left-hemisphere hypometabolism). Figure 4 shows a scatterplot and the regression of RT costs plus benefits on rCMR-glc asymmetry for the superior parietal region.

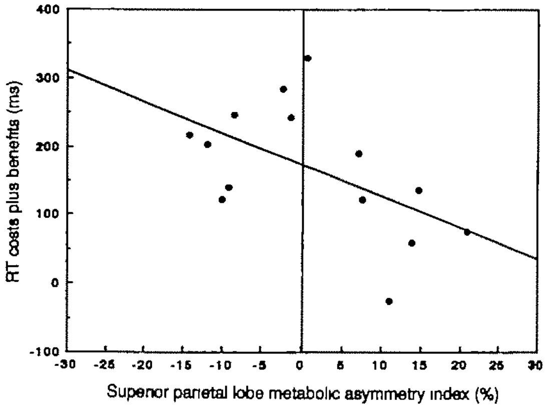

FIG. 4 Scatterplot and regression of mean RT costs plus benefits in the peripheral cue condition on right-left asymmetry in regional cerebral metabolic rates for glucose (rCMR-glc) in the superior parietal lobe.

To investigate whether metabolic asymmetry in the superior parietal lobe was associated with directionally specific disengagement deficits in DAT, correlations were computed between rCMR-glc asymmetry and the difference in median RT for invalid cue trials between targets in the right and left visual fields (taken over all SOAs because there were insufficient trials to compute median RTs reliably for left and right visual fields at each SOA). Because two asymmetry scores were associated, a positive correlation was expected. The correlation was 0.43 for central cues and −0.10 for peripheral cues. Neither correlation was significant. Thus, the disengagement deficit in DAT was marginally greater for the visual field contralateral to the hypometabolic hemisphere for the central cue condition but not for the peripheral cue condition.

Detection task reaction time

Both DAT and control subjects were highly accurate in the letter-detection task, error rates averaging 1.4% and 1%, respectively. Figure 5 shows mean RTs for both groups. Subjects with DAT had longer RTs than controls, F(1,28) = 16.2, $P < 0.001$. Significant effects were also obtained for Cue Validity, F(2,56) = 34.0, $P < 0.0001$, and SOA, F(2,56) = 26.6, $P < 0.0001$. All other sources of variance were not significant. Mean RT costs plus benefits (invalid cue RT−valid cue RT) for the DAT, and control groups were 66 ms and 38 ms, respectively. The corresponding values for the letter-discrimination task (which were significantly different) were 95 ms and 53 ms, respectively (central cues only). Despite the comparable magnitudes of these group differences, the non-significant Group × Cue Validity and Group × Cue Validity × SOA interactions indicate that cue validity effects did not vary between groups for the letter-detection task.

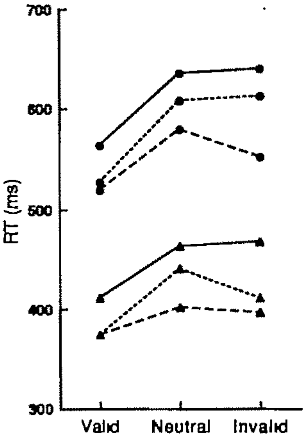

FIG. 5 Mean RT as a function of cue validity (valid, neutral, invalid) and SOA (——, 200 ms; ----, 500 ms; – – –, 2000 ms) in DAT patients (●) and controls (▲) for a simple letter detection task

Simple reaction time

The simple RT data were examined for differences between groups and blocks (beginning and end of session). There was a small increase in RT across the session, averaging about 9% across subjects. However, no significant differences emerged due to Group, Block or their interaction. Mean simple RTs were 412 ms and 365 ms for the DAT and control groups, respectively.

DISCUSSION

Focusing and disengagement of visuospatial attention in DAT

The results point to a pattern of intact and impaired functioning in DAT patients in component operations underlying shifts of visuospatial attention. Valid spatial location cues reduced RT to targets (compared with neutral cues) for both letter-discrimination and letter-detection tasks. Reaction time benefits were found for both peripheral cues that draw attention 'automatically' to the target location as well as for central cues that require a voluntary, more 'effortful' shift of attention (Posner, 1980; Jonides, 1981; Müller and Rabbitt, 1989). However, RT benefits conferred by either type of cue did not differ significantly between the DAT group and healthy, age-matched controls. Moreover, DAT patients could perform both tasks relatively accurately. These results indicate that DAT patients can use an advance cue to shift visuospatial attention to an expected location as effectively as age-matched controls. Under the conditions of the present study, therefore, attentional focusing by spatial location appears intact in the early stages of DAT.

In contrast to the effects of valid location cues, significant group differences were found for the effects of invalid location cues. Invalid cues incurred RT costs (compared with neutral cues) for both central and peripheral cues. With either cue type, the DAT group had significantly higher overall RT costs due to an invalid cue than the control group. This suggests a specific impairment in mild and moderate DAT in the ability to reorient or 'disengage' attention from an incorrect spatial location to another location

(Posner, 1980; Posner *et al.*, 1984*b*). The results confirm our first prediction that the attention-shifting impairment in DAT is specific to the effect of invalid location cues that require the disengagement of spatial attention, whereas the initial shifting of attention to an anticipated location is intact in mild to moderate DAT.

Group differences in speed-accuracy trade-off or in the effects of fatigue did not influence this pattern of intact attentional focusing and impaired attentional disengagement. The DAT group was significantly less accurate than the control group (although the ceiling accuracy level for the control group clouds the interpretation of the significant group difference). However, the DAT patients were able to perform both the peripheral and central cue tasks, as indicated by error rates of less than 9%; and their increased error rate does not affect the interpretation of the results for RT costs plus benefits. The increased error rate on this simple task that the DAT patients could comprehend and perform suggests sporadic fluctuations in alertness or in the ability to assess semantic knowledge regarding letters. With respect to fatigue, both DAT patients and controls showed some increase in simple RT across the session, but the group difference in RT costs was not linked to differences between groups in the effects of fatigue.

The selective impairment of visuospatial attentional switching appears specific to patients with parietal lobe damage (Posner *et al.*, 1984*b*), including patients with Alzheimer's dementia. It does not appear to be characteristic of aging or of neurodegenerative disorders in general. Using the same task as the present study, Greenwood *et al.* (1989) found relatively small increases in RT costs plus benefits between the ages of 20 yrs and 80 yrs in normal adults. Moreover, age-related effects were obtained only for central cues and not for peripheral cues, suggesting that automatic orienting is preserved in normal aging but not in DAT. Other studies have also found only small changes in cue-validity effects with normal aging (Nissen and Corkin, 1985; Hartley *et al.*, 1990). Patients with Parkinson's disease showed reduced RT costs due to invalid cues, suggesting an impairment in the maintenance of focused attention (Wright *et al.*, 1990), as opposed to the disengagement deficit for DAT patients. However, whether this deficit is specific to DAT or to dementia in general remains to be determined. The correlations between RT costs plus benefits and parietal lobe hypometabolism (*see below*) suggests that the attentional deficit may occur in any disorder that affects the functional integrity of parietal association cortex.

Mean RT costs plus benefits did not differ significantly between the DAT and control groups for the letter-detection task, unlike the letter-discrimination task. This may be due to the greater need for focal attention in the letter-discrimination task, which required a choice RT response to one of several letters, compared with the letter-detection task, where a simple RT response was required to the single letter X. The results for the detection task support the previous brief report by Nissen *et al.* (1981), who found that RT costs plus benefits were normal in DAT for a cue-target interval of 2000 ms. Nissen *et al.* (1981) also reported that DAT subjects showed neither costs nor benefits at an SOA of 3000 ms. Using the same task and SOAs as Nissen *et al.* (1981), Freed *et al.* (1989) reported that a subgroup of DAT subjects responded 'anomalously', having *faster* RTs to invalid cues than to valid cues, whereas others responded normally. Freed *et al.* (1989) suggested that the anomalous responders in the DAT group represented a subgroup of DAT with impaired selective attention linked to locus coeruleus pathology. No evidence of 'anomalous' responding was found in the present study for SOAs in the range

200–2000 ms, suggesting that the anomalous response pattern is not a general one. The phenomenon appears to be restricted to very long SOAs of 3000 ms or more. It may be particularly difficult for DAT patients to maintain attentional focus for periods of time as long as 3000 ms, by which time inhibitory processes may develop (Posner and Cohen, 1984), leading to a reduction in vigilance (Bahri and Parasuraman, 1989). Thus these results indicate that DAT subjects may have difficulties in sustained attention (Alexander, 1973; Parasuraman and Nestor, 1986; Sahakian *et al.*, 1989) in addition to selective attention deficits.

The finding that DAT subjects show normal RT benefits due to a valid location cue suggests that they can focus attention as effectively as normal subjects, i.e. that selection by location is normal in DAT. Nebes and Brady (1989) also reported that DAT patients could use colour cues to focus attention in a visual search task as well as normal age-matched controls, i.e. that selection by colour was normal in DAT. Do these results imply, therefore, that the operation of attentional selection in general is unimpaired in DAT? Not necessarily. Selection by location in the visuospatial attention task we used was relatively simple because stimuli were presented in an otherwise empty field. When targets are presented along with distractors in the visual field, selection is more difficult and greater benefits and costs of cue-directed attention are found (Müller and Findlay, 1988). Subjects with DAT may not be as efficient as normal subjects in location selection when the target must be 'filtered' from a field cluttered with several stimuli. Furthermore, attentional selection may be based on a number of attributes other than location; for example, elementary features such as colour and orientation, as well as more complex aspects such as form, grouping and category. While selection by a single feature such as colour may be normal in DAT subjects, selection on the basis of more complex stimulus features may be impaired (Nebes and Brady, 1989).

Time course of shifts in visuospatial attention

Our second hypothesis was that group differences in RT costs plus benefits would vary with cue-target interval or SOA and with cue type (central and peripheral). Specifically, we predicted that for peripheral cues, DAT subjects would show greater RT costs plus benefits than controls at shorter cue-target SOAs, whereas, for central cues, they would show greater costs plus benefits at longer SOAs. The results broadly conformed to the predictions. The pattern of RT benefits and costs obtained is consistent with the view that peripheral cues elicit an early automatic attentional orienting process, whereas central cues elicit a later 'effortful' orienting process (Jonides, 1981; Müller and Findlay, 1988; Müller and Rabbitt, 1989). The DAT group showed significantly greater costs plus benefits than controls at cue-target intervals less than 500 ms for peripheral cues and at intervals greater than 500 ms for central cues. Thus, in DAT automatic shifts of attention elicited by peripheral cues reveal abnormalities earlier than attention shifts initiated effortfully by central cues. These time course differences suggest that there may be different underlying mechanisms of attentional switching that are dysfunctional in DAT. Abnormalities for exogenously driven (automatic) orienting may reflect increased refractoriness (following an attention shift) at short SOAs. Because differences in centrally driven ('effortful') orienting occur at longer SOAs, they may reflect perseveration or reduced inhibition. Overall, the present results indicate that both forms of shifts in visuospatial attention, i.e. obligatory automatic shifts and voluntary effortful shifts, are affected in DAT, but that the abnormality is only manifest at specific time intervals depending upon cue type.

Neural systems of visuospatial attention

Our third hypothesis was that group differences in cue validity effects would be linked to resting levels of cerebral glucose metabolism in the superior parietal lobe for DAT patients but not for controls. We predicted that increased RT costs plus benefits in DAT patients would be related to relative hypometabolism in the right compared with the left superior parietal lobe. This prediction was partially supported. Negative correlations of -0.42 and -0.54 were obtained between right-left metabolic asymmetry and RT costs plus benefits for central and peripheral cues, respectively, with only the latter correlation being significant. Correlations were small and non-significant for other cortical areas (inferior parietal, prefrontal and occipital) and for all areas in the control subjects. Thus, as predicted, DAT subjects with lower right- than left-hemisphere metabolic rates (right-hemisphere hypometabolism) had higher RT costs plus benefits than DAT subjects with lower- than right-hemisphere metabolic rates (left-hemisphere hypometabolism).

The RT-metabolic correlations in the DAT group are consistent with the view that the right posterior parietal lobe has a dominant role in the control of spatially directed attention (Critchley, 1953; Heilman and Van Den Abell, 1980; Mesulam, 1981; Weintraub and Mesulam, 1987). Our finding that increased RT costs plus benefits were related to hypometabolism in the superior parietal but not inferior parietal lobe is consistent with the findings of Posner *et al.* (1984*b*) that patients with superior parietal lobe damage show deficits in the disengagement of spatially directed attention. Moreover, the correlation we obtained between right hemisphere hypometabolism in the superior parietal lobe and RT costs plus benefits is consistent with their finding of a greater disengagement deficit for right-lesioned than for left-lesioned patients. However, we did not obtain reliable evidence in favour of the prediction that the attention disengagement deficit in DAT is greater for targets presented contralaterally to the hypometabolic hemisphere than for ipsilateral targets, as was found by Posner *et al.* (1984*b*) for patients with focal left or right parietal lobe lesions. Perhaps this occurs reliably only when the parietal lobe lesion is unilateral. In patients with DAT, the parietal association cortices generally demonstrate bilateral hypometabolism that is asymmetric (Haxby *et al.*, 1985).

Our correlational results should not be taken to indicate that the visuospatial attentional disengagement deficit in DAT is necessarily due to hypometabolism of the superior parietal lobe in isolation. First, we obtained correlations between RT scores and resting cerebral metabolism, these two measures being recorded at different times. Associations between resting levels of brain metabolism and cognitive performance may occur only when both are affected by neurological disease, as in the present study, but stronger, more reliable associations may require that both sets of measures are obtained simultaneously, as in PET studies of changes in regional cerebral blood flow associated with cognitive activity. Recently, preliminary PET evidence has been reported for activation of posterior parietal cortex in normal human subjects engaged in a visuospatial attention-switching task (Petersen *et al.*, 1988). Secondly, it is likely that the attentional disengagement operation is not a function of the parietal cortex alone but involves the participation of other cortical and thalamic areas (LaBerge, 1990; Posner and Petersen, 1990).

Despite these caveats, the results are broadly suggestive of a link between the known pattern of cortical pathology in Alzheimer's disease and emerging knowledge on the cortico-cortical networks subserving directed visual attention (Goldman-Rakic, 1988; Posner and Petersen, 1990). Post-mortem studies have revealed that the Alzheimer's disease process affects pyramidal cells interconnecting neocortical association areas, including parietal and frontal cortices (Pearson *et al.*, 1985; Morrison *et al.*, 1990). There is growing evidence that a similar network of cortico-cortical connections between the posterior parietal and frontal lobes is involved in the control of shifts of visuospatial attention (Mesulam, 1981; Posner *et al.*, 1984*b*; Goldman-Rakic, 1988). The visuospatial attention-switching deficit in DAT may be related to dysfunction of some of these interconnected areas. Alternatively, the deficit may result from impaired interaction between the posterior parietal and frontal lobes. In an analysis of inter-regional functional associations in cerebral metabolism, Horwitz *et al.* (1987) found reduced correlations in resting metabolic rates between the posterior parietal lobe and the frontal lobe in DAT patients compared with healthy controls, suggesting that the disease process results in a functional uncoupling of these brain regions.

Conclusions

Cognitive deficits in patients with dementia have often been attributed to underlying impairment in attention-allocation processes (Lezak, 1983; Nebes *et al.*, 1984; Jorm, 1986; Grady *et al.*, 1989; Hartman, 1991; Nestor *et al.*, 1991*a*). Yet, until recently, the specific attention-allocation mechanisms that may be impaired in DAT have not been extensively studied. Because of the diversity of the cognitive deficits found, DAT has often been characterized as a 'global' cognitive disorder resulting from a generalized failure of DAT patients to mobilize and allocate attentional resources to cognitive operations. While such a global attentional deficit may be characteristic of severely affected patients, the present results suggest that in the mild to moderate stages the visuospatial attentional deficit in DAT is selective rather than global. Patients with DAT show similarly selective as opposed to global deficits in visuospatial memory tasks (Sahakian *et al.*, 1988). In the present study cue-directed attentional focusing to an anticipated location was intact, whereas the disengagement of attention was found to be impaired. The disengagement deficit was linked to relative hypometabolism in the superior parietal lobe of the right hemisphere of DAT patients.

These results have some general implications for understanding the pattern and developmental course of cognitive deficits in Alzheimer's disease. Memory problems are the first observable behavioural symptom of DAT. As such, memory constitutes the most important and widely studied area of cognitive deficit in DAT (Morris and Kopelman, 1986; Nebes, 1989). In contrast, although many investigators have pointed to the importance of attention in DAT, few studies of attentional functioning in DAT have been reported (Parasuraman and Nestor, 1986; Nebes and Brady, 1989; Nestor *et al.*, 1991*a,b*). The present results suggest that attention represents another important aspect of the cognitive impairment in DAT. Because attentional deficits appear relatively early in the course of Alzheimer's disease, they may also contribute to the development of deficits in other areas. It has been suggested, for example, that hippocampal and temporal lobe pathology, leading to memory loss, is followed by dysfunction of the parietal and frontal lobes, resulting in attentional deficits (Grady *et al.*, 1988; Haxby *et al.*, 1988, 1990). According to this view, deficits in memory and attention appear early and precede deficits in language, spatial skills, problem solving and other high-level cognitive functions. If attentional deficits do indeed precede these higher-order cognitive skills, then the frequently expressed sentiment that some cognitive deficits in DAT are due to underlying attentional problems (Nebes *et al.*, 1984; Ober *et al.*, 1985; Hartman, 1991) will have a more reliable empirical basis.

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WHITE MATTER LESIONS ON MAGNETIC RESONANCE IMAGING IN CLINICALLY DIAGNOSED ALZHEIMER'S DISEASE

EVIDENCE FOR HETEROGENEITY

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SUMMARY

In a prospective magnetic resonance imaging (MRI) study we evaluted the prevalence and severity of white matter changes in 29 patients with Alzheimer's Disease (AD) and 24 age-matched healthy elderly, all without cerebrovascular risk factors.

The AD patients were divided into two groups according to age at onset of symptoms, one with presenile onset AD (n = 13) and one with senile onset AD (n = 16), who were matched for dementia severity. Signal hyperintensities were rated using a semiquantative scoring method, separately in the periventricular region (PVH) and in the lobar white matter (WMH), as well as in the basal ganglia (BGH) and in the infratentorial region (ITFH). Cortical atrophy as a parameter of grey matter involvement was rated on a 0 (absent) to 3 (severe) scale.

We found PVH, WMH and BGH scores to be significantly higher in senile onset AD patients than in age-matched controls. By means of multiple linear logistic regression we found that PVH, WMH and BGH scores were significantly dependent on the diagnosis of senile onset AD, while the PVH score also showed a significant age dependency. Cortical atrophy did not differ significantly between presenile onset AD and senile onset AD patients.

These results indicate that presenile onset AD and senile onset AD patients differ with respect to white matter involvement, but not with respect to grey matter involvement on MRI. Since cerebrovascular risk factors were excluded these findings may indicate that senile onset AD patients display more small vessel involvement (arteriolosclerosis) than presenile onset AD patients, suggesting additional (microvascular) factors for the dementia syndrome in senile onset AD. Our data lend support to the growing body of evidence that AD is heterogeneous, consisting of at least two types. Based on our findings two forms can be distinguished: (i) a 'pure' form of the disease, usually with early disease onset, and no more white matter changes than normal for age; (ii) a 'mixed' form, usually with disease onset later in life, and showing more white matter changes on MRI than normal for age.

INTRODUCTION

Alzheimer's Disease (AD) is a degenerative disease characterized by cerebral atrophy with cortical and subcortical grey matter changes. Brun and Englund (1986), however, found symmetrical deep white matter changes at autopsy in more than 60% of patients

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with AD. Histopathologically these changes consisted of a partial loss of myelin, oligodendroglial cells and axons and mild reactive gliosis, in the absence of hypertensive vascular changes. They postulated that these changes were of cerebrovascular hypoperfusional/hypoxic origin (Englund *et al.*, 1988).

White matter changes in patients with dementia were recognized on computerized tomography (CT) (Erkinjuntti *et al.*, 1984; Rezek *et al.*, 1987) and were termed 'leuko-araiosis' (Hachinski *et al.*, 1987). They were also seen on magnetic resonance imaging (MRI) (Fazekas *et al.*, 1987; Johnson *et al.*, 1987). In general, they were often interpreted as being diagnostic for vascular dementia, in particular Binswanger's disease (Erkinjuntti *et al.*, 1984; Hershey *et al.*, 1987). However, white matter abnormalities were increasingly reported in AD too, but studies regarding the actual occurrence of white matter lesions in AD have yielded conflicting results. For instance, Fazekas *et al.* (1987), Rezek *et al.* (1987), Erkinjuntti *et al.* (1989), Kertesz *et al.* (1990) and Leys *et al.* (1991) found significantly more white matter changes in AD patients than in healthy controls, whereas Leys *et al.* (1990) and Kozachuk *et al.* (1990) failed to find any difference in white matter changes between these groups. The contribution of white matter changes to the clinical features of the dementia syndrome in AD is also still under debate (Gupta *et al.*, 1988; Rao *et al.*, 1989; Bondareff *et al.*, 1990; Kertesz *et al.*, 1990).

The differences in prevalence ranges can partly be explained by the use of different imaging modalities but we propose two other possible explanations. First, in most of the MRI studies the presence and severity of white matter hyperintensities were assessed by means of the Fazekas' rating scale (Fazekas *et al.*, 1987). This scale provides only global information contrary to the CT method of scoring leuko-araiosis (Rezek *et al.*, 1987). In addition, inter-observer reliability of the Fazekas method has been shown to be poor (Leys *et al.*, 1990, 1991). Secondly, in most of the imaging studies AD was considered to be one single disease entity. However, clinical, biochemical and neuro-imaging studies have shown differences between presenile onset AD and senile onset AD (Gottfries *et al.*, 1983, 1985; Rossor *et al.*, 1984; Wallin *et al.*, 1989; Blennow *et al.*, 1991). If the prevalence of white matter lesions differs between these subtypes of AD, this could explain the contradictory results of earlier studies. If substantiated, the combination of different clinical manifestations and different MRI findings would support the idea that presenile and senile AD are different disease entities and therefore require a different scientific approach and different therapeutic strategies (Gottfries, 1989*b*; Roth and Wischnik, 1985).

In this prospective study we investigated the prevalence and severity of white matter involvement in patients with early- and late-onset AD, who were matched for severity of dementia, using a newly developed semiquantitative rating scale. We also evaluated grey matter involvement by assessing cortical atrophy in both groups. Since white matter lesions are reported to be correlated with cerebrovascular risk factors and age (Awad *et al.*, 1986; Gerard and Weisberg, 1986), we used age-matched healthy elderly people for comparison, and we included only patients and controls without cerebrovascular risk factors.

SUBJECTS AND METHODS

Patients

Twenty-nine AD patients were included in the study. The diagnosis of probable AD was established according to the National Institute of Neurologial Disorders and Stroke-Alzheimer's Disease and Related

Disorders Association (NINCDS-ADRDA) criteria (McKhann *et al.*, 1984). To minimize the influence of cerebrovascular risk factors, we did not include patients with a history or signs and symptoms of cardiac disease. In addition, patients whose systolic blood pressure had ever been found to be higher than 140 mmHg, or whose diastolic blood pressure had been higher than 90 mmHg were not included. Fasting glucose blood levels had to be lower than 5.6 mmol/l and Hachinski's Ischaemic score had to be lower than, or equal to, 4 (Hachinski *et al.*, 1975). Laboratory studies, including serum chemistry testing, a complete blood cell count and differential cell count, vitamin B_{12} and folic acid levels and urin analysis, had to be normal. Finally, a CT-scan was made to exclude cerebral infarcts and other intracerebral pathology. None of the included patients had a conclusive family history of AD, and none of them displayed myoclonus or extrapyramidal signs. Histopathological confirmation of the clinical diagnosis AD was obtained in four patients.

According to the age at onset of symptoms (determined by comprehensive discussions with carers and spouses) the AD patients were divided into two groups: 13 with presenile dementia of Alzheimer type (presenile onset AD) and 16 patients with senile dementia of Alzheimer type (senile onset AD), with the demarcation at 65 yrs, in agreement with the NINCDS-ADRDA criteria. Severity of dementia was measured by means of the Mini Mental State Examination (MMSE) (Folstein *et al.*, 1975). There was no statistically significant difference in MMSE scores between presenile onset AD and senile onset AD patients (one-way ANOVA).

Controls

The control group consisted of 24 healthy volunteers. Some were enrolled from a project on 'successful aging' organized by the University, others were patients suffering from non-neurological disease, or relatives of the investigators, and one was the twin sister of a patient. Each of them had given informed consent after the nature of the procedure had been fully explained. Their selection depended upon the absence of the following criteria: positive family history of dementia; a history of brain disease or psychiatric disease; history or signs and symptoms of cerebrovascular disease, including arterial hypertension; use of any medication; an MMSE score below 27. They underwent the same clinical evaluation as the patient group, with the exception of a CT scan of the brain.

The controls were divided into two subgroups to match the presenile onset AD and senile onset AD groups in age, Norm 1 (n = 14) and Norm 2 (n = 10), respectively. The characteristics of patients and controls are given in Table 1. Statistical analysis failed to reveal any difference between the presenile onset AD and Norm 1 group, and between the senile onset AD and Norm 2 group, for (one-way ANOVA), and for mean blood pressure and mean blood glucose levels between the four groups (Kruskall-Wallis analysis of variance).

TABLE 1 SUBJECT CHARACTERISTICS

	Presenile onset AD group	*Control group Norm 1*	*Senile onset AD group*	*Control group Norm 2*
n	13	14	16	10
F/M	9/4	7/7	8/8	6/4
Age (years) ± SD	62.4 ± 6.5	63.8 ± 4.7	75.1 ± 3.8	73.9 ± 2.9
(Range years)	(52–69)	(54–69)	(68–81)	(70–80)
MMSE scores	13.2 ± 5.7	29.2 ± 1.0	15.0 ± 4.6	28.1 ± 0.9
(Range)	(5–23)	(27–30)	(6–21)	(27–30)

Methods

Magnetic resonance imaging was performed on a 0.6 T Teslacon superconducting magnet using multislice/multi-echo SE technique, with two excitations and a 1.6×1 mm in plane resolution. We used mildly T_2-weighted (TR 2500 ms, TE 60 and 120 ms) axial slices, with a slice thickness of 7.5 mm and a 25% interslice gap, and no flow compensation.

Signal hyperintensities were defined (at TE 60) as areas of higher signal intensity compared with brain tissue and cerebrospinal fluid, which have intermediate signal intensity at this TE, and were scored in a semiquantitative way. This scoring method produces a score related to both the size and number of foci with increased signal hyperintensity. Signal hyperintensities were scored in the following regions: (i) periventricular, in the frontal and occipital region and parallel to the lateral ventricles; (ii) lobar white matter, separately in the frontal, temporal, parietal and occipital region; (iii) the basal ganglia: caudate nucleus, putamen, globus palidus and thalamus; (iv) the infratentorial region: cerebellum, mesencephalon, pons and medulla. Scores of different brain regions were added to obtain the following sum scores: periventricular hyperintensities (PVH), white matter hyperintensities (WMH), basal ganglia hyperintensities (BGH) and infratentorial foci of hyperintensity (ITFH). Involvement of the subcortical U-fibres was noted as present or absent. The method is shown in detail in Table 2. Examples of different scores are given in Fig. 1A–G.

TABLE 2 VISUAL RATING OF MRI HYPERINTENSE LESIONS

Periventricular hyperintensities			
Caps.	Occipital	0/1/2	0 = absent
	Frontal	0/1/2	1 = ≤5 mm
			2 = ≥6 mm and ≤10 mm
Bands	Lateral ventricles	0/1/2	
		PVH =	
White matter hyperintensities			
	Frontal	0/1/2/3/4/5/6	0 = no abnormalities
	Parietal	0/1/2/3/4/5/6	1 = ≤3 mm, n ≤ 5
	Occipital	0/1/2/3/4/5/6	2 = ≤3 mm, n ≥ 6
	Temporal	0/1/2/3/4/5/6	3 = 4–10 mm; n ≤ 5
		WMH =	4 = 4–10 mm, n ≥ 6
			5 = ≥11 mm, n ≥ 1
			6 = confluent
Basal ganglia hyperintensities			
	Caudate nucleus	0/1/2/3/4/5/6	
	Putamen	0/1/2/3/4/5/6	
	Globus pallidus	0/1/2/3/4/5/6	
	Thalamus	0/1/2/3/4/5/6	
		BGH =	
Infra-tentorial foci of hyperintensity			
	Cerebellum	0/1/2/3/4/5/6	
	Mesencephalon	0/1/2/3/4/5/6	
	Pons	0/1/2/3/4/5/6	
	Medulla	0/1/2/3/4/5/6	
		ITFH =	

Cortical atrophy was rated (at TE 120) on a scale ranging from 0 (no atrophy) to 3 (severe atrophy) separately in the frontal, temporal, parietal and occipital regions. Magnetic resonance imaging scans were viewed by two experienced raters and scored according to the criteria outlined above when consensus was reached. Both viewers were blinded to the age and diagnosis of the subject.

Statistical assessment

Differences in the hyperintensity scores and cortical atrophy ratings were tested using the non-parametric Mann-Whitney U test. Multiple linear regression analysis was performd using a model including age and two so-called indicator variables, one for each dementia category, to establish the influence of these variables on the PVH, WMH and BGH scores. Data were analysed using the SPSS/PC™ statistical package P-values <0.05 were regarded as statistically significant. Null hypotheses were tested two sided.

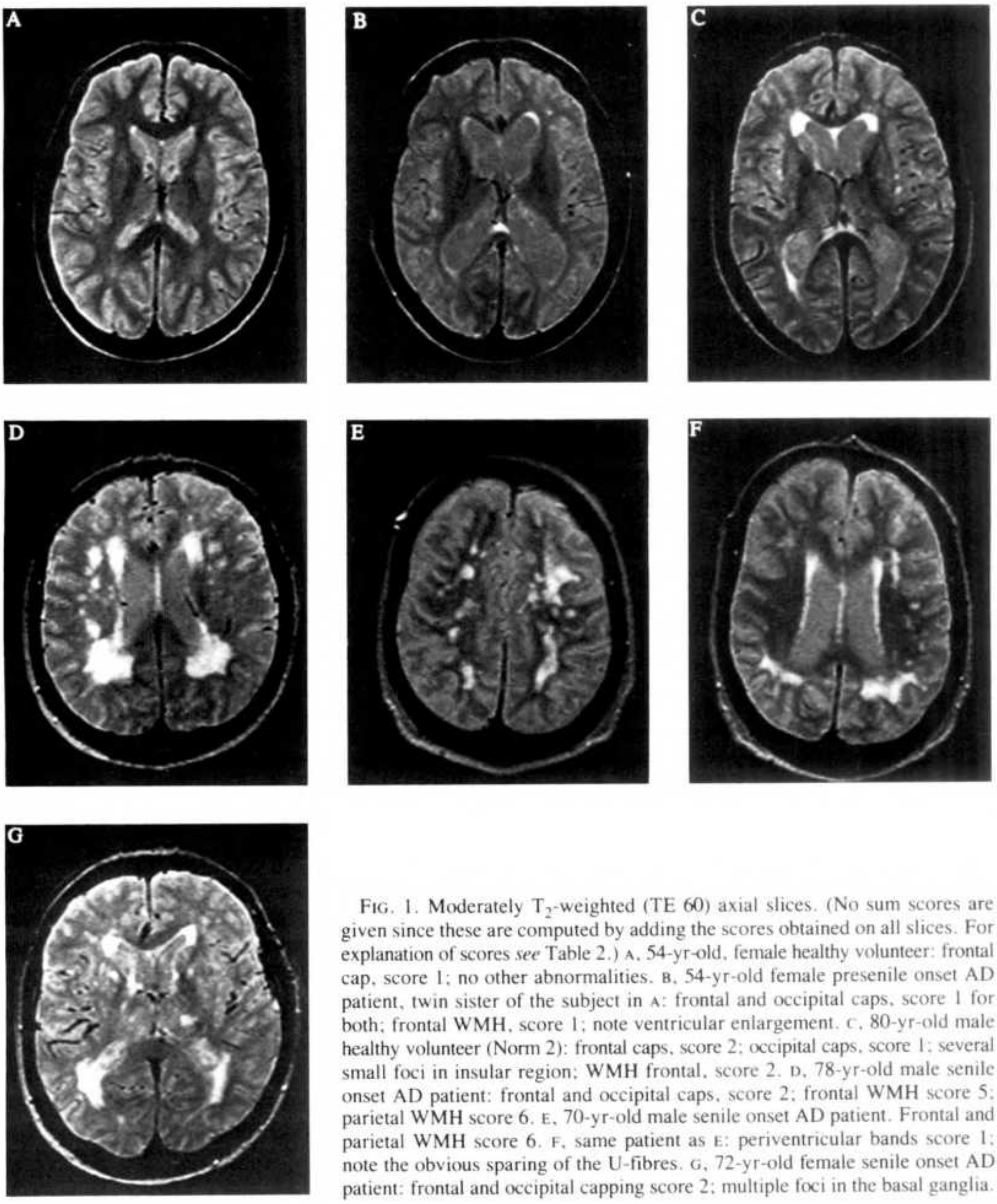

FIG. 1. Moderately T_2-weighted (TE 60) axial slices. (No sum scores are given since these are computed by adding the scores obtained on all slices. For explanation of scores *see* Table 2.) A, 54-yr-old, female healthy volunteer: frontal cap, score 1; no other abnormalities. B, 54-yr-old female presenile onset AD patient, twin sister of the subject in A: frontal and occipital caps, score 1 for both; frontal WMH, score 1; note ventricular enlargement. C, 80-yr-old male healthy volunteer (Norm 2): frontal caps, score 2; occipital caps, score 1; several small foci in insular region; WMH frontal, score 2. D, 78-yr-old male senile onset AD patient: frontal and occipital caps, score 2; frontal WMH score 5; parietal WMH score 6. E, 70-yr-old male senile onset AD patient. Frontal and parietal WMH score 6. F, same patient as E: periventricular bands score 1; note the obvious sparing of the U-fibres. G, 72-yr-old female senile onset AD patient: frontal and occipital capping score 2; multiple foci in the basal ganglia.

RESULTS

The MRI findings are summarized in Table 3. None of the images showed involvement of the subcortical U fibres. We found no significant differences in any of the hyperintensity scores between presenile onset AD patients and the Norm 1 group.

Statistically significant differences in the scores for the occipital caps, the bands adjacent

TABLE 3. SUMMARY OF MRI FINDINGS

		Presenile onset AD group (n = 13)	*Control group Norm 1 (n = 14)*	*P*	*Senile onset AD group (n = 16)*	*Control group Norm 2 (n = 10)*	*P*
Periventricular hyperintensities							
Caps:	Occipital	1 (0–1)	1 (0–2)	0.38	1.5 (1–2)	1 (0–2)	0.02
	Frontal	1 (1–2)	1 (1–2)	0.59	2 (1–2)	2 (1–2)	0.24
Bands:	Lateral	1 (0–1)	1 (0–1)	0.59	2 (1–2)	1 (1–2)	0.004
	(Sum score)	3 (1–4)	3 (1–5)	0.31	5 (3–6)	3.5 (3–5)	0.003
White matter hyperintensities							
	Frontal	2 (0–4)	1 (0–2)	0.17	4.5 (1–6)	2 (1–5)	0.004
	Parietal	1 (0–5)	1 (0–2)	0.48	2 (0–6)	1 (0–3)	0.02
	Occipital	0 (0–6)	0 (0–1)	0.47	1 (0–6)	0 (0–3)	0.11
	Temporal	0 (0–1)	0 (0–1)	0.56	0 (0–5)	0.5 (0–2)	0.81
	(Sum score)	4 (0–9)	2 (0–5)	0.09	8.5 (4–21)	3.5 (1–10)	0.003
Basal ganglia hyperintensities							
	(Sum score)	0 (0–3)	0.5 (0–2)	0.41	2 (0–6)	0 (0–3)	0.004
Infra-tentorial foci of hyperintensity							
	(Sum score)	0 (0–3)	0 (0–3)	0.33	0.5 (0–8)	0 (0–6)	0.22

Median (minimum–maximum) of white matter scores in disease groups and controls. *P*-values for differences are given (Mann-Whitney U test).

to the lateral ventricles and the PVH (sum) score were found between senile onset AD patients and the Norm 2 group. We detected significant differences between senile onset AD patients and the Norm 2 group in frontal and parietal lobar white matter scores, and in the total WMH score. The BGH score differed significantly from controls, while the ITFH score did not.

In Fig. 2A,B,C the actual number of patients in each group displaying a certain sum score of WMH, PVH and BGH is given, together with the median score of each group. In Table 4 the frequency of lobar white matter scores higher than 1 in each region for the four groups is shown. The highest frequency is found in senile onset AD patients in the frontal and parietal white matter.

The results of the multiple regression analysis are summarized in Table 5. As can be seen in Table 5A, PVH scores depended significantly on age ($P = 0.028$). Corrected for age the PVH scores for presenile onset AD did not differ significantly from controls, whereas the age-corrected average PVH score for senile onset AD patients differed significantly from controls ($P = 0.0002$). From the regression coefficients and the covariance matrix of the estimates (not shown) the age corrected difference in PVH scores between presenile onset AD and senile onset AD can be calculated. We found that PVH scores were higher in senile onset AD patients than in presenile onset AD patients ($P = 0.002$).

As can be seen in Fig. 2B, WMH scores show more variance (scatter) among senile onset AD patients than among presenile onset AD patients and controls. To allow for this inequality in variance a weighted multiple regression was performed (Snedecor and Cochran, 1980). The results of this weighted regression are shown in Table 5B. The

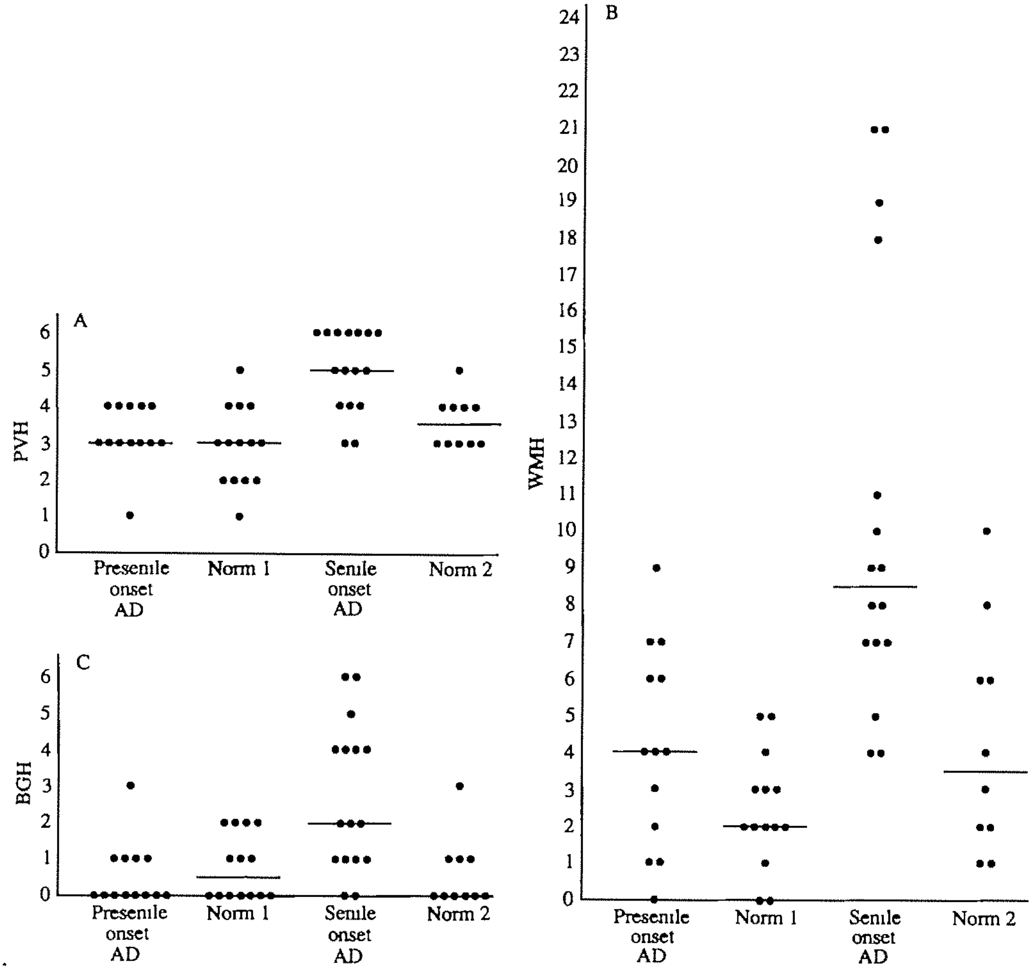

FIG. 2. Scatter graphs showing the number of subjects in the four groups and their respective PVH total scores (A), WMH sum of scores (B, and BGH sum of scores (C) The horizontal lines represent the median scores. (The median scores for BGH in presenile onset AD and Norm 2 were zero.)

results for WMH are the same as those for PVH, except that there is no significant age dependency ($P = 0.24$). The age-corrected difference in WMH scores between senile onset AD and presenile onset AD was significant ($P = 0.006$).

The results for the BGH scores show great similarity to the WMH results (Table 5c). The age-corrected difference in BGH scores between senile onset AD and presenile onset AD was significant ($P = 0.004$).

The difference in cortical atrophy between the AD patients and controls reached statistical significance in both the temporal and frontal regions. We failed to find a significant difference in cortical atrophy in any of the four regions between presenile onset AD and senile onset AD patients.

TABLE 4 NUMBER OF PATIENTS (PERCENTAGE) DISPLAYING A SCORE WMH HIGHER THAN 1

	Presenile onset AD group (n = 13)	*Control group Norm 1 (n = 14)*	*Senile onset AD group (n = 16)*	*Control group Norm 2 (n = 10)*
White matter hyperintensities				
Frontal	6 (46)	5 (36)	14 (88)	4 (40)
Parietal	4 (31)	3 (21)	12 (75)	3 (30)
Occipital	2 (15)	0 (0)	6 (37)	1 (10)
Temporal	0 (0)	0 (0)	3 (19)	1 (10)

TABLE 5

Variable	*Coefficient*	*SD*	*P*
A. Results of regression analysis on PVH			
Age	0.05	0.02	0.028
Presenile onset AD	0.32	0.35	0.37
Senile onset AD	1.42	0.35	0.0002
B. Results of weighted regression analysis on WMH			
Age	0.08	0.06	0.24
Presenile onset AD	1.39	0.96	0.16
Senile onset AD	6.74	1.63	0.0001
C. Results of regression analysis on BGH			
Age	0.01	0.03	0.66
Presenile onset AD	−0.09	0.50	0.86
Senile onset AD	1.88	0.49	0.0001

DISCUSSION

Using semiquantitative assessment of signal hyperintensities we found higher white matter scores and basal ganglia scores in senile-onset AD than in presenile AD and age-matched controls. Grey matter involvement (cortical atrophy) proved to be equal in both demented groups.

We used a scoring system in which periventricular and subcortical white matter hyperintensities as well as the hyperintensities in the region of the basal ganglia and infratentorial region were rated separately. Risk factor analyses and results of functional studies have suggested different aetiologies for subcortical white matter foci and periventricular 'caps and bands' (Fazekas *et al.*, 1987; Kertesz *et al.*, 1988; Fazekas, 1989; Kobari *et al.*, 1990). Therefore, a distinction in scoring seems appropriate, but is not generally applied (Brant-Zawadzki *et al.*, 1985; Kertesz *et al.*, 1990). Additionally, contrary to a global score provided by the Fazekas score, our method produces regional, surface-based information with optimal use of high sensitivity MRI to detect minimal changes in the white matter. We will discuss our findings further below with respect to the different localizations of the hyperintense foci and with respect to possible heterogeneity of AD.

Periventricular hyperintensities

In agreement with preceding reports (Sze *et al.*, 1986; Zimmerman *et al.*, 1986; Drayer, 1988; Fazekas, 1989; Hendrie *et al.*, 1989) we found a significant dependency on age for PVH. Sze *et al.* (1986) have shown that high signal intensity around the frontal horns (caps) may be explained by (an age-related) loss of ependyma in the frontal horns, with subsequent increased water content in the local brain parenchyma. Similar findings were reported recently by Leifer *et al.* (1990). Our results, however, are contrary to those of McDonald *et al.* (1991) and Fazekas *et al.* (1987) who reported higher PVH scores (rated with the Fazekas' system) in a presenile AD group, compared with age matched controls. The latter authors, however, could themselves not replicate these findings in another study (Fazekas *et al.*, 1991). Both ours and Fazekas' scoring method suffer from overlap between PVH and WMH scores, when large caps are present. Arbitrarily, we rated large caps exceeding 10 mm as WMH, in our study, to avoid rating them twice, both as PVH and WMH (*see* Fig. 1). Yet, the difference between presenile onset AD and senile onset AD patients in the occipital caps and PVH scores we found, may still partly result from an overlap with WMH scores in the occipital and parietal white matter.

White matter hyperintensities

Subcortical and deep white matter hyperintensity scores, especially in the frontal and parietal regions, were significantly higher in the senile onset AD group than in the age-matched control group. An explanation for this regional predominance might be that these areas are overrepresented on axial slices, compared with the relatively small occipital area. Rating signal intensities in the temporal region was troubled by flow artefacts. Since no flow compensating gradients were used, possible differences between groups were less detectable.

By means of multiple regression analysis we were able to show a significant dependency of the sum score WMH on the diagnosis of senile onset AD versus presenile onset AD, unrelated to the differences in age. This means that WMH scores in senile onset AD patients were higher than could be expected for their age.

There may be several explanations for this. First, although we rigorously excluded vascular risk factors in all subjects and all patients had Hachinski scores ranging from 0 to 4, the senile onset AD patients may contain some patients with mixed dementia. It has been argued earlier that demented patients who exhibit low Hachinski scores may represent AD patients, or may be suffering from Binswanger's disease or in fact all other vascular dementias without clinically evident strokes (O'Brien, 1988). In the study by Mölsä *et al.* (1985) 50% of the pathologically proven mixed cases had Hachinski scores lower than 5. Results from functional studies have indicated that the presence of leuko-araiosis is associated with decreased cerebral blood flow in patients with multi-infarct dementia as well as in senile onset AD patients (De Reuck *et al.*, 1991). Secondly, WMH probably result from a subacute hypoperfusion/hypoxic process (Ferrer *et al.*, 1990), and higher scores may reflect the presence of more severe cerebral amyloid angiopathy (Gray *et al.*, 1985; Scheinberg, 1988; Janota *et al.*, 1989; Haan *et al.*, 1990) or some form of neurogenic vasculopathy induced by AD, as suggested by Scheibel *et al.* (1987). On the other hand, cerebral amyloid angiopathy is not reported to differ considerably between early and late onset AD (Vinters, 1987), and severe cerebral amyloid angiopathy often produces brain haemorrhage (Vinters, 1987; Haan *et al.*, 1990), which was not present in any of our patients. We were able to obtain pathological confirmation of the diganosis AD in four senile onset AD patients. In all, the (frontal) white matter showed arteriolosclerosis with severe loss of axons and demyelination, in the absence of hypertensive changes and amyloid angiopathy, in agreement with earlier findings (Brun and Englund, 1986; Van Swieten *et al.*, 1991). Thirdly, Wallerian degeneration has been put forward as the origin of WMH by Leys *et al.* (1991) and Leifer *et al.* (1990). If this were the case, one would expect more involvement of the subcortical U-fibres. In addition, cortical atrophy was the same for presenile onset AD and senile onset AD, suggesting equal grey matter involvement, which also makes Wallerian degeneration less likely as the causative factor for WMH.

Basal ganglia hyperintensities

Another interesting finding of our study comprises the significantly higher BGH scores in senile onset AD patients, unrelated to age differences. In view of our definition of signal hyperintensities, identified at TE 60, these represent real hyperintensities and not lacunes or Virchow Robin spaces. Similar lesions may be seen on MRI scans of patients with Binswanger's disease but the absence of cortical lesions virtually rules out this diagnosis (Révész *et al.*, 1989). However, hyperintensities in these regions have been mentioned as an argument in favour of coexistence of vascular and Alzheimer's dementia (Tatemichi, 1990). They may have been missed in earlier studies since other rating scales do not identify such lesions.

Infratentorial foci of hyperintensity

No differences were found in the hyperintensity scores of the infratentorial region between the four groups. This may be due to the fact that grading signal hyperintensities in this region is troublesome. Moreover, this region is commonly not affected in AD.

Heterogeneity of Alzheimer's disease

Our findings again raise the question as to whether AD constitutes one or several diseases (Gottfries, 1989*a*). Despite variations in clinical presentation (disturbed language functions, extrapyramidal signs, mood disturbances), AD is still considered to be one single disorder because of the neuropathological similarities (neurofibrillary tangles and senile plaques in the neocortex) in all types. However, clinical and psychiatric observations (Burns *et al.*, 1990; Blennow *et al.*, 1991) as well as neurochemical studies (Rossor *et al.*, 1984; Gottfries *et al.*, 1985; Svennerholm *et al.*, 1987) have provided evidence that AD consists of at least two disorders, with different ages at onset. We have not investigated whether differences in white matter involvement would contribute to clinical differences between subtypes of AD, as suggested by Englund *et al.* (1989) and Kertesz *et al.* (1990), since we matched our dementia groups on the basis of clinical disease severity, thus creating groups only differing in the age at onset of disease.

In reports in which CT and MRI have been used to detect white matter changes in AD, a distinction between presenile onset AD and senile onset AD has generally not been made. This may explain why some authors report small differences in white matter changes between AD patients and normal elderly (Rezek *et al.*, 1987) and others do not (Kozachuk *et al.*, 1990; Leys *et al.*, 1990). For example, in the study of Leys *et al.* (1990) in which 17 AD patients were included, of whom 14 had presenile onset, no differences in white matter changes between AD patients and normal controls were shown. Their results are in agreement with our study, but their conclusion is only applicable to the presenile form. Wallin *et al.* (1989) and Blennow *et al.* (1991) demonstrated a difference between early and late onset AD with respect to white matter involvement, using CT. Given the fact that leuko-araiosis on CT correlates well with WMH on MRI (Hachinski *et al.*, 1987; Leys *et al.*, 1990), our results are comparable with theirs. However, they did not include age-matched controls, hence their findings may be secondary to age differences alone.

Our scoring system shows that grading white matter lesions is not straightforward, which makes comparison with other studies difficult. If we arbitrarily decide that a score higher than 1 (*see* Table 2) may be considered 'severe', then a majority of senile onset AD patients (88%) shows severe frontal white matter involvement, in contrast to a minority of the presenile onset AD (46%) patients (Table 4). If the origin of these abnormalities is indeed 'a small vessel disease', e.g. arteriolosclerosis with chronic ischaemia (van Swieten *et al.*, 1991), in order to select a homogeneous group of AD cases for research purposes and evaluations of therapeutic strategies, MRI should be added to exclude patients displaying severe white matter changes. However, no studies investigating the origin of white matter hyperintensities specifically in AD patients have been reported yet, and normative data for white matter hyperintensities in healthy elderly subjects without cerebrovascular risk factors should be provided first.

Our data confirm that one has to be cautious in diagnosing patients with white matter lesions, as 'senile dementia of Binswanger's type' as suggested by Román (1987). These lesions may be present in patients fulfilling research criteria for probable AD, and even in healthy elderly persons without any of the clinical features ascribed to Binswanger's disease (Bennett *et al.*, 1990).

In conclusion, our findings lend support to the growing belief that clinically diagnosed AD is heterogeneous, probably consisting of 'pure' and 'mixed' cases, the latter usually with later disease onset and displaying more white matter signal hyperintensities on MRI than normal for age, suggesting other (microvascular) contributing pathogenetic factors.

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PURE AMNESTIC SEIZURES IN TEMPORAL LOBE EPILEPSY

DEFINITION, CLINICAL SYMPTOMATOLOGY AND FUNCTIONAL ANATOMICAL CONSIDERATIONS

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SUMMARY

Pure amnestic seizures (PAS) sometimes occur in patients with temporal lobe epilepsy. They never represent the only type of seizures in these patients. Pure amnestic seizures are defined as seizures during which the only clinical manifestation is the patients' inability to retain in memory what occurs during the seizure coupled with the preservation of other cognitive functions and the ability to interact normally with their physical and social environment It is postulated that PAS result from selective ictal inactivation of mesial temporal (MT) structures without isocortical involvement. This occurs most often in patients with neuropsychological and electroencephalographic (EEG) evidence of bilateral dysfunction of MT structures (six out of eight patients in this study). In the few patients without such evidence as well as in some with bilateral MT dysfunction, PAS may result from seizure discharge limited to the MT structures of both temporal lobes. In the light of current anatomical knowledge, contralateral spread of seizure discharge from the MT structures of one side to those of the other through the dorsal hippocampal commissure is the only likely explanation for this situation. One observation with depth electrode stimulation of MT structures supports this view. In patients with evidence for bilateral MT dysfunction, a unilateral seizure may presumably suffice to induce a PAS, the contralateral MT structures being unable to ensure normal memory function. In most instances PAS can be distinguished from episodes of transient global amnesia on clinical grounds.

INTRODUCTION

In 1986 when critically examining the adequacy of 'loss' or 'impairment of consciousness' as the determining criterion for defining complex partial seizures (Bancaud *et al.*, 1981), one of us (P.G.) emphasized the difficulties that arise when one attempts to use this concept for probing the underlying mechanism of these attacks (Gloor, 1986). 'Loss' or 'impairment of consciousness' in a complex partial seizure is usually a compound phenomenon. Commonly its two most salient features are unresponsiveness and amnesia. Both are far from simple and one may occur without the other. The terms 'loss' or 'impairment of consciousness' camouflage a variety of disturbances of higher nervous function. However, these can often be identified and teased apart by carefully observing

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the patient and by interacting with him during a seizure, and sometimes also by careful history taking. In that earlier study the hope had been expressed that such analyses may help to identify different underlying mechanisms and anatomical substrates of complex partial seizures. It was surmised, for instance, that ictal amnesia may either result from bilateral spread of temporal lobe seizure discharge or, in the case where the discharge remains unilateral, may denote an incapacity of the contralateral hippocampal region to sustain adequate memory function.

The present paper is an attempt to determine the usefulness of this approach. For this purpose we have selected for study a small number of patients suffering from complex partial seizures of temporal lobe origin in whom some of the attacks were characterized by a selective loss of memory for events occurring during the seizure with no other clinical ictal manifestations being evident. We shall call such attacks pure amnestic seizures (PAS). We wished to examine what characterizes patients who exhibit PAS from the point of view of their interictal memory function and what inferences concerning functional anatomy could be drawn from these neuropsychological data and from electroencephalographic (EEG) findings. We shall also discuss the differential diagnosis of these seizures, particularly with respect to transient global amnesia.

MATERIALS AND METHODS

Patient population

The study group, Group 1, consisted of eight patients known to be afflicted with complex partial seizures who at one time or another had exhibited one or several PAS. Only patients whose history had been obtained personally by one of us (P.G.) were included in order to ensure that all of them satisfied strict criteria for PAS. We did not feel confident that these could be met by perusing descriptions recorded in hospital charts.

To be rated as a PAS it was necessary for the patient to have had a well-documented complete loss of recollection for whatever happened during the seizure and for whatever he or she did at that time. Furthermore, there had to be equally satisfactory documentation that the patient's responsiveness to persons and events around him/her was fully preserved during the attack and that there was no obvious confusion or speech disturbance. Thus, patients were able during such seizures to engage in whatever activities appeared appropriate at the time. This implied that apart from the ability to record in memory what went on, their cognitive functions remained intact, including the ability to rationally appraise the situation they were in. Consequently their behaviour during the seizure was not considered abnormal by the people around them at the time.

It should be emphasized that in none of the eight patients with PAS, was this their only or even their most common seizure type. All had at other times more conventional complex partial seizures with unresponsiveness, confusion, amnesia and other features characteristic for temporal lobe attacks.

Because we were interested in the possible underlying functional anatomical substrate of these seizures, and because we suspected that some form of bilateral mesial temporal (MT) dysfunction was most likely present in PAS, we compared the patients of Group 1 (with PAS) to two other groups of patients, Groups 2 and 3, none of which had a history of PAS, although all had ictal amnesia associated with unresponsiveness and confusion in most of their seizures.

Group 2 consisted of 10 patients with a clinical history of complex partial seizures suggestive of temporal lobe origin who were randomly selected from 150 patients investigated with stereotaxically implanted depth electrodes, because they had shown evidence for bilateral independent epileptiform abnormalities in their surface EEGs. Invasive EEG investigations with depth electrodes confirmed the presence of bitemporal independent interictal epileptiform discharges and showed that in some of these patients seizures originated from one temporal lobe, and in others from both.

Group 3 consisted of 10 patients with a history of complex partial seizures of presumed temporal lobe origin who were randomly selected from 100 patients who had undergone intensive extracranial EEG investigation in the 18 mths preceding the study. Extracranial EEG investigations showed only unilateral temporal interictal epileptiform disturbances and seizure onset from the side of the interictal focus. No patient in this group had undergone invasive EEG studies.

All 28 patients in the three groups suffered from medically intractable seizures and were considered candidates for surgical therapy.

Electroencephalographic studies

All patients underwent a thorough EEG, radiological and neuropsychological work-up. Informed consent for all procedures was obtained from all of them. Extracranial 16-channel EEGs were recorded repeatedly in all patients by means of scalp and sphenoidal electrodes, using the 10–20 electrode system. In the 12 patients in whom intracerebral depth electrodes were used, these were stereotaxically implanted bilaterally into the temporal and frontal lobes (Gloor *et al.*, 1982). The deepest contacts of these electrodes sampled the amygdaloid, anterior and mid-hippocampal regions and mesial frontal cortex. The more superficial contacts recorded from overlying isocortical regions, both at the brain surface and in the depths of sulci. In the frontal lobe usually the orbitofrontal, cingulate, supplementary motor areas and dorsolateral convexity cortex were explored. All patients with surface or depth recordings were subjected to intensive monitoring by 16-channel cable telemetry and video recording which incorporated automatic spike and seizure detection programs (Gotman *et al.*, 1985).

Computerized tomography (CT) scans with and without contrast injection (EMI 1010, Picker 1200SX, GE 9800) were obtained in all patients. Seventeen of the patients also had magnetic resonance imaging (MRI) scans performed on a superconductive magnet (Philips Gyroscan S15) operating at field strengths of 0.5 Tesla in four patients and 1.5 Tesla in the other 13 patients who had MRI scans with T_1- and T_2-weighted, as well as inversion recovery images.

Neuropsychological studies

Neuropsychological evaluation, including noninvasive memory assessment, was performed in all patients according to a protocol designed at our institution (Milner, 1975). Memory performance was evaluated according to known hemispheric specialization for memory function: memory for verbal material is processed predominantly in the speech-dominant temporal lobe, while memory for nonverbal material, such as abstract designs or faces, is dependent mainly on the homologous structures on the nondominant side (Milner, 1978, 1990; Jones-Gotman, 1987).

Certain aspects of memory reflecting isocortical-hippocampal interactions are believed to be similarly lateralized (e.g. Milner, 1965; P. Corsi, 1972, unpublished thesis; Petrides, 1985; Jones-Gotman, 1986), and a hippocampal role has been reported by some authors for tasks used in the present study. Thus Rausch and Babb (1987) reported and Sass *et al.* (1990) confirmed impaired learning, assessed on the Wechsler Memory Scale (WMS) (Wechsler, 1945), which uses paired words ('Associate Learning'), in patients with significant cell loss from CA1 and parahippocampal gyrus on the left. Also, Katz *et al.* (1989) found impaired memory for WMS-R prose passages ('Logical Memory') (Wechsler and Stone, 1987) in patients with greater mesial resection from the left temporal lobe as measured by quantitative postoperative MRI. They also found impaired memory for WMS geometric drawings ('Visual Reproduction') in those with greater resection from the right mesial temporal structures.

For the present study we have considered memory dysfunction to be lateralized to the dominant MT region when the patient failed verbal memory tests, and to the nondominant one after failure on tests of memory for designs. Tests used were Logical Memory, Associate Learning and Visual Reproduction from the WMS, and recall for the Rey-Osterrieth complex figure (Rey, 1941; Osterrieth, 1944). Although these are not the most powerful measures available for lateralizing dysfunction in individual cases (Jones-Gotman, 1991), we have used them because all of the patients had received those tests. Only delayed measures were used. For each patient, the scores from the Logical Memory and Associate Learning were combined to form a verbal recall score, for which an impairment cut-off was set at 12 or less. A single design recall score was also used, combining the WMS Visual Reproduction and the Rey-Osterrieth figure, cut-off for impairment on this was 11.

Hemispheric dominance for language was estimated, based on a detailed handedness questionnaire and on the results of dichotic listening tests: in most (22 of the 28 cases) it was determined by intracarotid sodium Amytal testing. Memory function was also assessed during this test in order to determine whether both, only one or neither side was capable of sustaining adequate memory function. The Amytal tests were performed according to a protocol described elsewhere (Jones-Gotman, 1987).

Patients were considered to have evidence for bilateral dysfunction of MT structures if they satisfied at least one of the following conditions: (i) deficits on both verbal and nonverbal noninvasive measures; (ii) severe memory dysfunction after both left- and right-sided injection of sodium Amytal; (iii) a lateralized pattern as evidenced by either verbal or nonverbal memory dysfunction according to noninvasive testing, but MT dysfunction contralateral to that lateralization according to the Amytal test; (iv) unilateral memory dysfunction according to either form of memory testing but onset of seizures from the temporal lobe contralateral to the side of memory dysfunction. If on the contrary only verbal or only nonverbal memory dysfunction was detected, the Amytal test demonstrated a corresponding unilateral MT dysfunction, and the EEG also showed that the seizures originated from that same side, i.e. if all evidence was concordant, it was concluded that the patient had unilateral dysfunction of MT structures.

Overall analysis of the results

Contingency table analysis was used to compare Group 1 patients (patients with PAS) with the two control groups (Groups 2 and 3) in terms of lateralization of MT dysfunction according to the combined analysis of noninvasive memory testing, Amytal testing and side of seizure onset. Statistical significance was accepted if $P < 0.05$. Factorial ANOVA was used to assess the statistical significance of differences in continuous values (age and duration of epilepsy) among the three groups.

RESULTS

Case reports on patients of Group 1

Patient 1. This 30-yr-old woman had seizures that started with either no aura, or with a warm sensation in both feet ascending through the legs. In most attacks this was followed by loss of contact, staring and fumbling automatic movements.

In one seizure during EEG-video monitoring using extracranial electrodes, she was reading a magazine when the seizure discharge started in the EEG (Fig. 1). She stopped reading and made some rubbing movements with her right hand. A few seconds later the phone beside her bed rang. She sat up, took the receiver and engaged in the following conversation: ‘Hello . . . Ça va bien? . . . Je veux rien que savoir si vous êtes arrivé. Ah, O.K. . . . Rien, je me couche, puis je dors. . . . Oui, non, non, c'est correct. . . . Bye-bye.’ She then lay down and covered herself with the blanket. During the entire telephone conversation, ictal activity was recorded from both temporal regions, mostly in the left mesial temporal region with a lesser involvement of the right (Fig. 1); it ended only after she had lain down. The next morning she did not recall having received a phone call. When confronted with the video replay of her seizure she was incredulous. She remembered that she had been reading a magazine, but had no recollection whatsoever of her telephone conversation. We succeeded in tracking down the caller, her cousin. He told us that their conversation had been entirely normal. He had not noticed anything amiss with the patient.

This patient allegedly had had meningitis in early infancy. Inerictal epileptic EEG abnormalities were localized to the left temporal lobe, and her MRI scan showed an increased signal in the left mesial temporal lobe region on T_2-weighted images.

Patient 2. This 36-yr-old woman had seizures ushered in by a sensation in her chest. In most of her seizures this was followed by staring, lip-smacking and garbled speech. When she tried to talk during these episodes her speech was sometimes incomprehensible. In some of her seizures, however, her behaviour was essentially normal. In one such

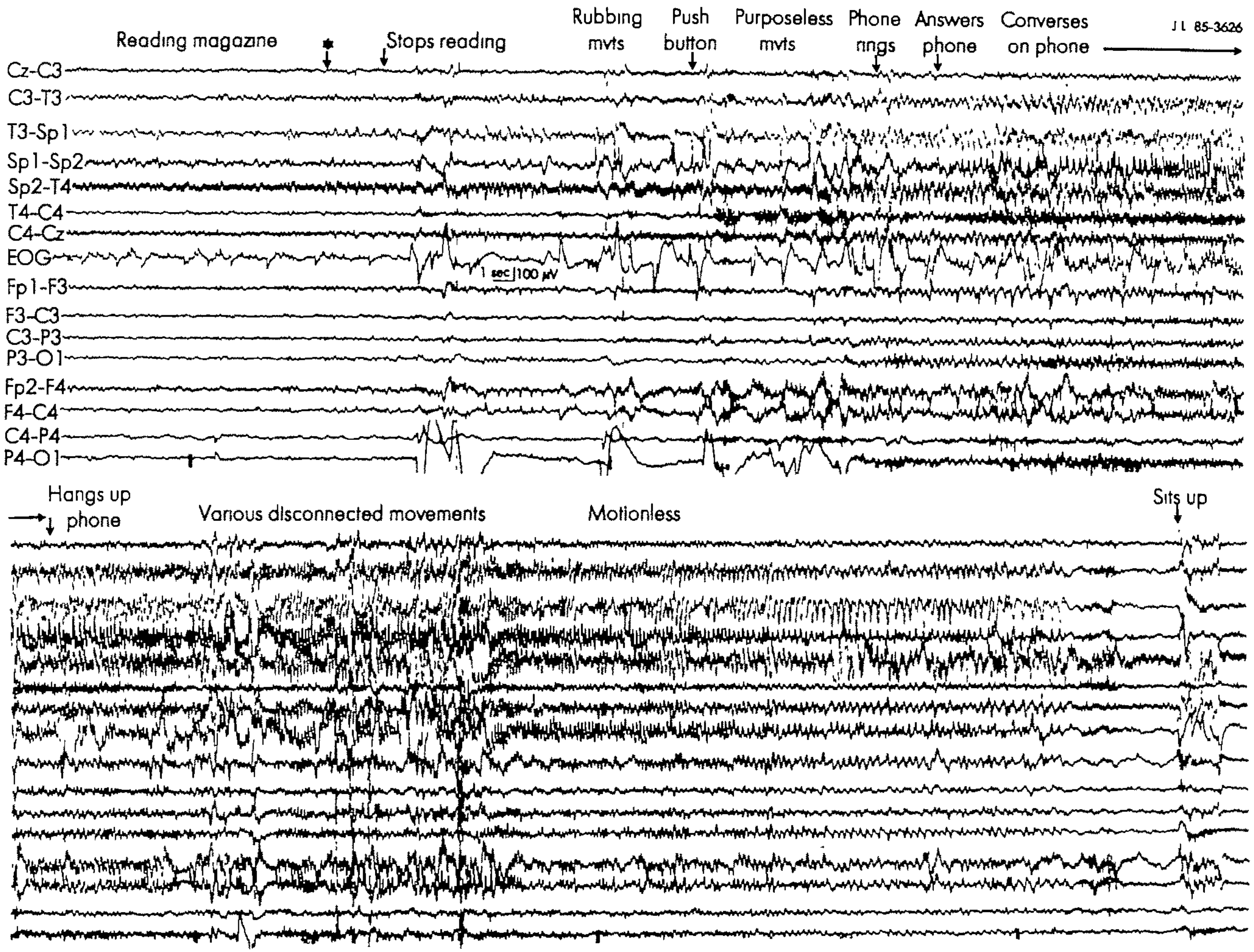

FIG. 1 Pure amnestic seizure recorded during long-term EEG-video-audio monitoring in patient 1. Surface EEG recordings were made with scalp and sphenoidal electrodes. Electrode positions are labelled according to the International 10–20 System (SP: sphenoidal electrodes). Seizure onset is indicated at the asterisk. Seizure discharge starts in the left temporal region and involves predominantly the MT region (phase reversal at Sp 1). It later spread to the left parasagittal region and ultimately also to the right hemisphere. EOG = electro-oculogram The lower panel is a direct continuation of the upper one For details of the phone conversation, *see* text. [From Gloor (1991*a*), reproduced with permission from Raven Press.]

episode she was transcribing from stenography into a word processor. She suddenly realized that she had a blank in her memory and did not remember having written the copy she saw on the computer monitor. She then read back what she had written and it was all correct, with the exception of a single typing error. The length of the material she had transcribed without remembering was about two to three paragraphs.

Another instance happened when she was shopping. Coming out of a store she realized that she had a blank in her memory, but must have written a cheque, because she had jotted down the amount in her cheque-book. She returned to the store to verify the fact that she had written a cheque, and found that she had done so correctly.

The only aetiological factor that could be found was a positive family history of epilepsy. Neuroimaging investigations with CT were normal. A volumetric MRI study showed smallness of the left amygdala and hippocampus. Her extracranial EEGs showed bitemporal independent epileptic discharges.

She was then studied with depth electrodes stereotaxically implanted into both temporal lobes, supplemented with epidural electrodes over the temporal convexity. The sodium Amytal test showed that she had bilateral MT dysfunction and an anomalous representation of speech which resided in the right hemisphere. Depth electrode recordings revealed that seizures could originate either from the left or right limbic structures. They either remained confined to one side or spread to the contralateral side, always to the limbic structures first. No PAS could, unfortunately, be documented during depth electrode recordings. Significant overt clinical manifestations occurred only in seizures in which seizure discharge had spread to involve right temporal isocortex whether in the course of a unilateral right-sided seizure or after spread of the ictal discharge from the left temporal lobe. The clinical manifestations consisted of dysphasia and some degree of unresponsiveness. With electrical stimulation of the left amygdala a seizure was induced which reproduced some aspects typical for PAS and gave some evidence that might be pertinent for its mechanism. The initial phase of the attack involved only the left-sided limbic structures with some subsequent modest spread to the left-sided temporal isocortex (Fig. 2). Subsequently the seizure spread to involve the right side as well. However, it spread initially to the right hippocampus only, and only seconds later to the right amygdala and right temporal isocortex (Fig. 2). The patient's behaviour remained entirely normal during the time the seizure involved only the left temporal lobe. She was vivacious and in full contact with us, named pictures correctly and repeated a test phrase correctly, knew where she was and gave the time of day approximately correctly. Yet after the seizure she had not the slightest recollection of any of these items, even when confronted with the correct ones amidst foils. This first part of the seizure thus fulfilled the criteria for a PAS. As the seizure spread to the other side, particularly once the right temporal isocortex became involved, her behaviour changed dramatically. She lost her vivaciousness, became slow in responding (even nonverbally), and at times was virtually unresponsive. She still made some eye contact with interlocutors, but was aphasic. She subsequently recalled nothing of this second part of the seizure.

Later in the course of depth electrode stimulation, limbic stimulations succeeded in evoking seizure discharges that remained confined to one or the other temporal lobe. They predominantly involved MT structures, but the patient showed no evidence of amnesia. Thus in this patient bilateral ictal involvement of MT structures seemed to be required to produce anterograde amnesia, probably coupled with some short-span

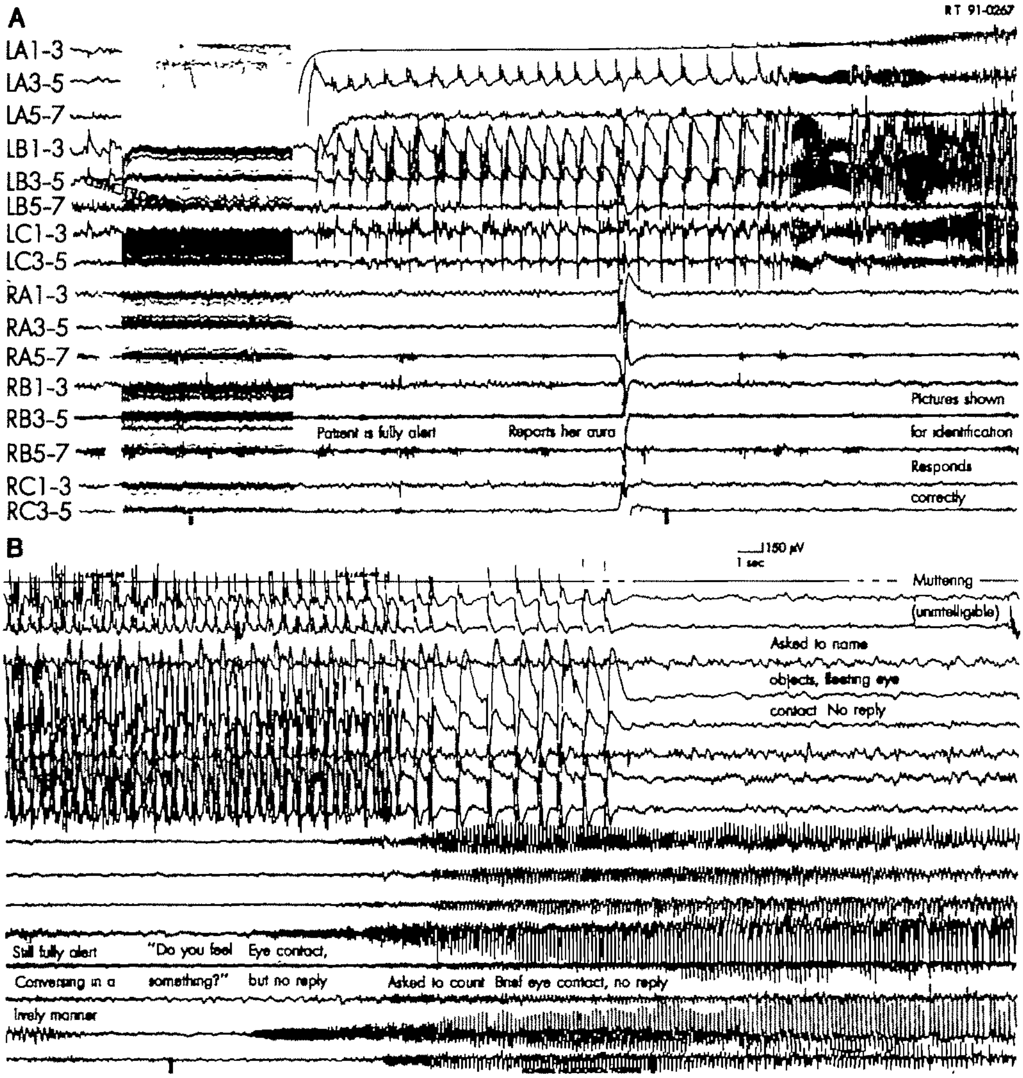

FIG 2 Patient 2. Response to electrical stimulation of the left amygdala (0.75 ma, 60 cps, 0.5 ms, biphasic square waves) for approximately 7 s (period covered by artefact in panel A). Panel A, there is electrical afterdischarge involving the left MT structures (LA1−3, LA3−5, LB1−3, LB3−5, LC1−3, LC3−5) with no spread to the superficial isocortical contacts (LA5−7, LB5−7) during which the patient behaves and responds entirely normally Panel B (which starts after a gap of 58 s) shows the spread of afterdischarge to the contralateral temporal lobe, first to the hippocampus (RB1−3, RC1−3), then to the amygdala (RA1−3) and shortly thereafter to the more superficial right temporal isocortex (LA5−7, RB5−7). The patient became verbally unresponsive and was aphasic The depth electrodes were inserted horizontally through the second temporal convolution Contacts 1 were mesial, the others at distances of 5 mm more superficially Contacts LA1−3, RA1−3, left and right amygdala, LB1−3, RB1−3, left and right rostral hippocampus, LC1−3, RC1−3, left and right parahippocampal gyrus and body of hippocampus For further explanations, *see* text.

retrograde amnesia for events of the initial phase of the seizure during which discharge had been unilateral and she seemingly had been in full command of her mental capacities.

Patient 3. This 44-yr-old woman had seizures starting with a feeling of 'things going away and then coming back close again', which she likened to a sensation of dozing off. In most of her attacks this was followed by loss of contact, paleness and repetitive automatic movements, like stirring coffee in her cup or the food on her plate. In some attacks, however, she felt her habitual aura, but continued to behave in an apparently normal fashion. In one instance, she was riding a bicycle when she had a warning. She was able to step off the bicycle and then push it along, but was amnestic from then on. She entered a department store with her bicycle, was stopped by an employee and obeyed his instructions to leave the store. After the attack she had no recollection of these events. On another occasion she went to a store to buy a coat. She was about to leave without paying, but when she was reminded that she had not paid she returned the coat and later was amnestic for the whole episode. (It can be argued that this patient had some confusion during these two episodes, since she engaged in some socially objectional behaviour. The store employees, however, did not consider her behaviour pathological and since she willingly and promptly complied with their requests, whatever confusion there had been must have been minimal. We therefore included this patient in the study group.)

No aetiological factors could be identified. The CT and MRI scans showed no structural lesions. Interictal extracranial EEGs showed bitemporal independent epileptic discharges. Recordings with depth electrodes disclosed that more than 80% of her seizures originated from the left temporal lobe. No PAS were recorded.

Patient 4. This 44-yr-old man had two types of complex partial seizures, one occurring only during daytime and the other during sleep. In the daytime attacks, for which he had no warning and which he called 'blackouts', he was usually able to carry on with some kind of activity which by itself looked normal to everyone else. However, later he realized that he had no memory of what he had done. On one occasion, he was in the cafeteria at his working place, where he had to present a card and sign a register to pick up his meal. After having eaten he presented himself a second time and ate lunch twice. That same afternoon the cook phoned and upbraided him for having eaten two meals. He had no recollection of having done so. The night-time seizures were characterized by moaning, lip-smacking and chewing followed postictally by inappropriate laughter and bizarre behaviour with thrashing movements.

No aetiological factors could be established. A CT scan done some years prior to his admission had been normal. An invasive EEG investigation was carried out at another centre and was complicated by a left temporal cortical haemorrhage. Its sequel was evident on the MRI done at our institution. His extracranial EEG studies showed bitemporal independent epileptic discharges. Depth electrode investigation demonstrated that most of the patient's night-time attacks originated simultaneously from both temporal lobes, with some left-sided predominance. No daytime seizures were recorded.

Patient 5. This 52-yr-old woman had seizures most often preceded by a 'familiar thought', which was always the same, but which she could not identify. This was not, however, a classical *déjà vu* illusion. On other occasions the aura was different and consisted of a feeling in her stomach like being on a roller-coaster. Most of her seizures then proceeded with a grunting vocalization, loss of contact, stiffness in the face and staring. At times she would fall. Occasionally, however, she had a different kind of seizure. In one of these, she was having lunch in the cafeteria of the Montreal Museum of Fine Arts and then found herself walking on Sherbrooke Street near the museum with her coat on and carrying her suitcase. She realized she must have claimed these from the enquiry desk where she had deposited them before entering the museum. She had no recollection of having done so. In another seizure she had correctly paid for an item in a store with her credit card but had no memory of this.

She had a history of a prolonged febrile convulsion at 3–4 mths of age. Her MRI scan showed an atrophic left hippocampus, and extracranial EEG investigation disclosed bitemporal interictal epileptiform discharges, with a left-sided predominance.

Patient 6. This 23-yr-old man had seizures starting with an unpleasant abdominal sensation, at times associated with a feeling of fear. In his habitual seizures he would have a glassy look in his eyes, chew and spit, and raise one or both arms. In some attacks he was able to keep in contact and communicate with people around him. His fiancée observed that when she asked him to do certain things during a seizure, he would carry out these instructions correctly, but later could not remember having done so. In one of these attacks he had said to his fiancée 'I am going to marry you, honey', but had no recollection of this after the attack. In some other seizures the patient would say to whoever was around 'I love you' and would attach the correct name of that person to that phrase. Thus, in one such episode he said to the patient next to him 'I love you, David', even though he had known David for only 1½ days. He had no recollection of this.

He had had a prolonged seizure at the age of 2 yrs which apparently had not been associated with fever. His extracranial EEG investigation showed right temporal epileptiform discharges and only minimal independent discharges in the left temporal region. He had a normal CT scan.

Patient 7. This 32-yr-old man had seizures usually preceded by a *déjà vu* illusion described as a feeling as if he 'had already seen this before', even if this involved novel places and people. The seizures would then habitually proceed with vocalization, chewing, picking up objects and eventually head-turning to either side. In some seizures, however, he was able to behave normally and take appropriate decisions. In one of them, for instance, he had his warning whilst driving.He was able to continue driving and park his car in a safe place. He had no recollection of this nor of how he had reached the place where he had parked his car.

No aetiological factors could be identified. The CT scan showed a right posterior temporal lesion, and the extracranial EEGs disclosed bitemporal spiking with marked right-sided predominance.

Patient 8. This 24-yr-old woman had seizures beginning at the age of 8 yrs, shortly after a car accident in which she sustained a skull fracture. She reported an aura which she described as a feeling 'as if in a dream'. This was followed by staring, unresponsiveness, lip-smacking, licking of the lips and rocking back and forth. A few attacks, however, were associated with preserved responsiveness and normal behaviour. In one of them, when she was working as a waitress, she was able to compute a customer's bill accurately and to bring him the correct amount of change. She then realized she had a blank in her memory and could not recall her interaction with that customer. She verified her calculations and realized that she had charged him correctly.

Her neuroradiological investigation was negative, and the extracranial EEG recordings disclosed right temporal epileptiform discharges.

Additional clinical data on the three groups of patients

Ages of onset and duration of the epilepsy, sex ratio and presence of an aura for the three groups are shown in Table 1. There was no significant difference in terms of age, of seizure onset or duration of epilepsy between the three groups (ANOVA, $P = 0.30$ and 0.50, respectively). In Groups 2 and 3, nine patients had auras, and one of Group 1 did not. The full-scale IQ varied from 85 to 119. A summary of relevant information for all Group 1 patients is presented in Table 2. Note that four patients had bilateral and four unilateral temporal interictal epileptiform discharges in extracranial EEGs, and three had atypical speech representation. Two patients in Group 2 also had atypical speech representation, but none did in Group 3.

Table 3 shows information on memory function, speech representation and side of seizure onset for all patients of the three groups. For the noninvasive memory tests, the conclusion (unilateral, bilateral or no dysfunction) drawn from the patient's pattern of memory results is shown, together with the deviations from the two cut-off scores. Thus zero or negative numbers represent impairments, while positive numbers depict scores that were above the cut-offs and therefore considered to be within normal limits.

TABLE 1 DEMOGRAPHIC DATA AND PRESENCE OF AURA

Group	*No.*	*Male : female ratio*	*Mean age at seizure onset (range) (yrs)*	*Mean duration epilepsy (range) (yrs)*	*Presence of aura (in no. of patients)*
1	8	3 : 5	15.0 (2–27)	21.5 (9–33)	7
2	10	7 : 3	12.2 (1–22)	17.8 (7–35)	9
3	10	5 : 5	10.0 (1–25)	24.3 (9–40)	9

Noninvasive memory testing (Tables 2, 3, 4)

Table 4 compares the three groups of patients with regard to noninvasive memory testing. The proportion of Group 1 patients with PAS who had both verbal and nonverbal memory dysfunction (bilateral abnormalities) was greater than that of Group 3 (unilateral temporal group), but similar to that in Group 2 (bilateral temporal group).

Amytal memory testing (Tables 2, 3, 5)

Twenty-two of the 28 patients had sodium Amytal tests, but in three of them (two patients in Group 2 and one in Group 3) only unilateral injections were performed.

Table 5 compares the three groups with regard to both Amytal memory testing and noninvasive memory testing. When the final lateralization was determined by only one of the two tests, either because the other was not performed or because in the Amytal test only one side was evaluated, this is indicated in the table. It again shows that more

TABLE 2 SUMMARY OF FINDINGS IN PATIENTS WITH PAS (GROUP I)

Patient no Handedness	*Age at seizure onset (yrs)*	*Duration epilepsy (yrs)*	*Aetiologic factors*	*Imaging studies*[1]	*Aura*	*Interictal EEG*[2]	*Ictal EEG*	*Amytal memory result*[4]	*Amytal language dominance*	*Noninvasive memory testing*[5]
(1) Ambidextrous	15	15	Neonatal meningitis	MRI-lesion left temporal	Warm feeling in both feet	Left temporal	Left temporal	Bilateral dysfunction	Bilateral R > L	Bilateral dysfunction
(2) Left	6	30	Positive family history	MRI-small left amygdala and hippocampus	Chest sensation	Bitemporal independent	Bitemporal[3]	Bilateral dysfunction	Left	Bilateral dysfunction
(3) Right	27	17	Unclear	CT/MRI normal	Feeling of dozing off	Bitemporal independent	Left temporal[3]	Bilateral dysfunction	Right	Bilateral dysfunction
(4) Right	20	15	Unclear	MRI-lesion left temporal	None	Bitemporal independent	Bitemporal[3]	Right dysfunction	Left	Right dysfunction
(5) Right	19	33	Febrile convulsion	MRI atrophy left hippocampus	Forced thought	Bitemporal independent	Bitemporal	No dysfunction	Left	Bilateral dysfunction
(6) Left	2	21	Prolonged seizure in childhood	CT normal	Epigastric sensation	Right temporal	Right temporal	Right dysfunction	Bilateral R = L	Bilateral dysfunction
(7) Right	23	9	Unclear	CT-lesion right temporal	*Déjà vu*	Bitemporal independent	Right temporal	No dysfunction	Left	Right dysfunction
(8) Ambidextrous	8	22	Head trauma	CT normal	' . . as if in a dream	Right temporal	Right temporal	n a	n a	No dysfunction

[1] Only the most informative study is indicated, [2] extracranial studies, [3] depth EEG, [4] all patients (except when n a) had bilateral injections, [5] lateralization refers to verbal and/or nonverbal memory dysfunction in relation to hemispherical dominance n a = not applicable

TABLE 3 SUMMARY OF EXTENT OF MESIAL TEMPORAL DYSFUNCTION ACCORDING TO DIFFERENT PARAMETERS

	Patient no.	*Speech representation*	*Temporal lobe of seizure onset*	*MT dysfunction on Amytal tests*	*MT dysfunction on noninvasive memory tests*	*Deviation from verbal cut-off*	*Deviation from design-score cut-off*
Group 1 (PAS)	3	Left	Left*	Bilateral	Bilateral	No scores available, reported bilateral from Sweden	
	5	Left	Bilateral	No dysfunction	Bilateral	−2.5	−2.0
	4	Left	Left*	Right	Right	+9.5	−4.0
	7	Left	Right	No dysfunction	Right	+9.5	−1.0
	8	Left	Right	n.a.	No dysfunction	+10.0	+3.5
	1	Bilateral R > L	Left	Bilateral	Bilateral	−2.0	−5.0
	2	Right	Bilateral*	Bilateral	Bilateral	−3.5	−3.5
	6	Bilateral R = L	Right	Right	Bilateral	−4.0	−5.0
Group 2 (bitemporal)	9	Left	Left*	No dysfunction	Right	+2.5	−3.0
	10	Left	Left*	Bilateral	Bilateral	−5.0	−6.0
	11	Left	Left*	No dysfunction	Right	+4.5	−3.5
	12	Left	Right*	Right	Bilateral	−4.0	−6.0
	13	Left	Right*	No left dysfunction**	No dysfunction	+8.5	+0.25
	14	Left	Right*	Left**	Right	+4.0	−1.5
	15	Left	Right*	No dysfunction	Bilateral	0	−4.0
	16	Left	Right*	Right	Right	+2.0	−1.25
	17	Bilateral L > R	Right*	Left	Bilateral	−0.25	−6.0
	18	Bilateral L > R	Right*	No dysfunction	Bilateral	−0.5	−3.75
Group 3 (unilateral)	19	Left	Left	n.a.	No dysfunction	+1.25	−6.0
	20	Left	Left	n.a.	Bilateral	−2.0	−4.0
	21	Left	Left	No right dysfunction**	Bilateral	−3.0	−7.5
	22	Left	Left	No dysfunction	Bilateral	−6.0	−3.25
	23	Left	Right	n.a.	No dysfunction	+2.75	+1.25
	24	Left	Right	No dysfunction	No dysfunction	+3.0	+1.25
	25	Left	Right	n.a.	Right	+4.25	−3.75
	26	Left	Right	n.a.	Right	+4.5	−3.5
	27	Left	Right	No left dysfunction**	No dysfunction	+4.25	+6.75
	28	Left	Right	No dysfunction	Right	+1.0	−3.75

*Depth EEG, **unilateral Amytal injection only, n.a. = not applicable.

TABLE 4 MESIAL TEMPORAL DYSFUNCTION ACCORDING TO NONINVASIVE MEMORY TESTING

	Bilateral	*Unilateral*	*None*	*Percentage bilateral*
Group 1 (PAS) n = 8	5*	2**	1	62
Group 2 (bitemporal) n = 10	5	4	1	50
Group 3 (unitemporal) n = 10	3	3	4	30

*Two patients with unilateral temporal interictal epileptiform abnormalities, **one patient with bitemporal interictal epileptiform abnormalities and one with unilateral spiking on the side of MT dysfunction suggested by noninvasive memory testing.

patients with PAS (Group 1) had evidence for bilateral dysfunction of MT structures than those in the unilateral control group. On this score approximately the same proportion of patients in the PAS (Group 1) and bitemporal group (Group 2) showed evidence for bilateral MT dysfunction.

TABLE 5 MESIAL TEMPORAL DYSFUNCTION ACCORDING TO AMYTAL AND NONINVASIVE MEMORY TESTING

	Bilateral	*Unilateral*	*None*	*Percentage bilateral*
Group 1 (PAS) n = 8	5 (3a, 2b)	2 (1a, 1b)	1	62
Group 2 (bitemporal) n = 10	6 (1a, 4b, 1d)	3 (1a, 2b)	1 (1b)	60
Group 3 (unitemporal) n = 10	3 (3b)	3 (3b)	4 (2a, 2b)	30

a, on account of both tests; b, on account of noninvasive tests only; c, on account of Amytal tests only, d, on account of discordant findings; left according to Amytal, right according to noninvasive tests.

Memory testing and ictal EEG (Tables 3, 6)

Since depth electrode studies have shown that most temporal lobe seizures originate in MT structures (Gloor *et al.*, 1982; Babb *et al.*, 1984) in which subsequently a sclerotic hippocampus is usually found (Babb *et al.*, 1984), we used the side of seizure onset as an additional indicator of MT dysfunction.

The ictal EEG findings were used in a combined analysis with the results of both neuropsychological test procedures.

Table 6 shows the results when the three lateralizing factors (evidence for MT dysfunction by noninvasive, by Amytal memory testing and by side of seizure onset) are combined. Thus, in a given patient evidence for bilateral MT dysfunction was assumed to be present when one of the following constellations of diagnostic findings was identified: (i) bilateral MT dysfunction from either on noninvasive memory testing, or on Amytal memory testing or on both combined; or (ii) unilateral MT dysfunction on either form of memory testing combined with seizure onset from the contralateral temporal lobe. On this basis six of the eight patients (75%) in Group 1, eight of the 10 (80%) in Group 2, but only three out of 10 (30%) in Group 3 had evidence for bilateral dysfunction of MT structures. Thus, Group 1 (PAS) was similar to Group 2 (bitemporal), but both were significantly different from Group 3 (unitemporal) patients ($P = 0.04$). In one patient of Group 1 (PAS) and in two of Group 2 (bitemporal) the Amytal test showed MT dysfunction lateralized to the side contralateral to the side of seizure onset. This was taken as evidence for bilateral MT dysfunction. Thus when a patient presents with a history of unequivocal PAS, the chances are high that MT structures on both sides are dysfunctional. The incidence is, however, less than 100%.

TABLE 6 LATERALIZATION OF MESIAL TEMPORAL DYSFUNCTION ACCORDING TO AMYTAL TESTING, NONINVASIVE MEMORY TESTING AND SIDE OF SEIZURE ONSET*

	Bilateral	*Unilateral*	*Percentage bilateral*
Group 1 (PAS) n = 8	6	2	75
Group 2 (bitemporal) n = 10	8	2	80
Group 3 (unitemporal) n = 10	3	7	30

*Includes all patients in each group: $\chi^2 = 6.19$, $P = 0.04$.

DISCUSSION

Characterization of PAS compared with other amnestic episodes in temporal lobe seizures

Amnesia for ictal and early postictal events in temporal lobe seizures is common. It is, however, usually coupled with unresponsiveness and confusion. The underlying cause of unresponsiveness is not always the same: it may be aphasia, the inability to initiate voluntary movements, sometimes perhaps a diversion of attention by a hallucinatory experience or some other ill-defined inability to respond to verbal or other stimuli (Gloor, 1986). In most of these instances it appears likely that seizure discharge has spread widely and interfered with the function not only of MT structures but also with that of temporal and extratemporal isocortex, usually by spread of ictal activity into these structures as suggested by our observations with depth electrode recordings in patient 2. Confusion is hard to define in strict terms. It probably occurs when elementary perceptual capacities are preserved, and when interference with isocortical function in temporal and frontal association cortex by spreading seizure discharge renders the patient incapable of using percepts in ways that are appropriate to the momentarily prevailing situation (Gloor, 1991*a*). We thus make the assumption that such full-blown manifestations of temporal lobe seizures as unresponsiveness and confusion indicate spread of the seizure discharge to isocortical areas.

By contrast, based on what is known about the anatomical substrate of amnesia both in humans and animals (Milner, 1970, 1978; Mishkin, 1982; Squire, 1986; Zola-Morgan *et al.*, 1986; Amaral, 1987), we postulate that this manifestation of temporal lobe epilepsy primarily indicates ictal interference with the function of mesial temporal structures, particularly that of the hippocampus. To become clinically evident this interference must either occur bilaterally, or it must affect the MT structures contralateral to those rendered nonfunctional by a static lesion (Gloor, 1986).

The present study documents observations on seizures in which the only ictal seizure manifestation was anterograde amnesia with full preservation of responsiveness and no evidence of any significant degree of confusion. We applied the term PAS to this type of seizures. Seizures of this kind have been described before (Penfield and Mathieson, 1974). The most famous case is that of Hughlings-Jackson's patient, Dr Z. (Hughlings-Jackson, 1889), who during a seizure that occurred while he was examining a patient made a diagnosis of lower lobe pneumonia, which he jotted down on a piece of paper. Later, when realizing that he had no recollection of having examined the patient, Dr Z. checked his notes and upon re-examining him found his diagnosis to have been correct.

Our patients showed ictal memory disturbances that were similar to those reported by Dr Z. Anterograde amnesia was the main or exclusive behavioural abnormality during the seizure, but the patients interacted in a normal way with other people and their environment; there was no unresponsiveness, no dysphasia, no apparent confusion, and no automatism. (In retrospect, because he has no recollection of what he did during the seizure, the patient or his physician may, however, erroneously conclude that the episode was one of automatism!)

The memory disturbance during PAS is akin to the anterograde memory deficit seen in amnestic patients. Such patients have no difficulty carrying on a normal conversation (like our patient 1) and are capable of performing tasks that require keeping track of what one is doing (like our patient 8). Their short-term memory, or 'primary memory', to use William James' (1899) term, is intact for as long as they are not distracted, but that memory is irretrievably lost as soon as the subject's attention shifts to a new topic. This type of memory disturbance is typical for patients with bilateral MT lesions, such as the famous patient H.M. (Milner, 1985). We therefore surmise that the memory disturbance in PAS results from bilateral loss of MT function.

In addition, there is evidence suggesting that in spite of the ictal anterograde amnesia there is no retrograde amnesia for events prior to the seizure during PAS, since during the attacks the patients seem to have access to previously formed memories, even to recent ones. Thus, for instance, during one of his attacks, our patient 6 appropriately used the name of his room-mate even though he had known him for only 1½ days. Furthermore, our patient 5 was able to find the enquiry desk at the Montreal Museum of Fine Arts during a PAS, even though, being a resident of Toronto, she could not have been very familiar with the museum and most likely learned the location of the enquiry desk only on the occasion of her visit when she had her PAS. In another patient, whose case is summarized in an earlier publication by Gloor (1986), and is not included in the present study because she had more florid temporal lobe seizure manifestations than those compatible with the diagnosis of PAS, we were able to document that she had no retrograde amnesia during the early part of her seizure for which she was later amnesic. At a time when she was already unresponsive (because of aphasia), she frantically tried to push the 'seizure button', obviously remembering the instruction we had given her a short time before that it was important to do this whenever she experienced a warning of a seizure. After the seizure she had no recollection of having done this.

This dissociation of anterograde and retrograde amnesia suggests that the mechanisms responsible for recording current items in memory and those responsible for retrieval of previously stored items may to some extent be separate. We tentatively suggest that the first of these functions is more tightly coupled to the hippocampus proper in the light of the observation of Zola-Morgan *et al.* (1986) on patient R.B. in whom the sector CA1 had been destroyed bilaterally by an anoxic insult and who suffered from anterograde amnesia with little or no evidence for retrograde memory difficulties.

Anatomical substrate for PAS

We postulate that in PAS the seizure discharge must result in a bilateral functional inactivation of MT structures, but spare the isocortical temporal structures, otherwise the ictal symptomatology would not be restricted to anterograde memory loss. The data summarized in Table 6 show that the majority (six out of eight) of patients with PAS indeed had evidence of bilateral dysfunction of MT structures when the data from noninvasive and invasive memory testing and from the lateralization of seizure onset were combined. In only one patient was such bilateral dysfunction attributable to the fact that the seizure discharge involved the side contralateral to that to which memory testing had localized a static MT dysfunction responsible for the memory deficit. In the light of these criteria Group 1 patients with PAS are very similar to those with proven bilateral temporal lobe dysfunction as represented by our Group 2, but they are very different from those who have unilateral temporal EEG foci in extracranial recordings. We can conclude from this that eliciting a history of PAS is highly suggestive of bilateral damage to MT structures, even if ultimately seizure onset can be demonstrated to be lateralized to one temporal lobe. In performing a unilateral temporal lobectomy, one must therefore assume that a potential risk for significant postoperative memory difficulties exists in these patients if the removal includes hippocampal tissue.

The mechanism of the ictal memory loss in PAS none the less remains uncertain. We had originally assumed that if demonstrable bilateral MT dysfunction is present, unilateral ictal inactivation of the hippocampal region may be sufficient to produce a PAS. This is probably true for some but not all patients. It certainly does not explain why PAS occurred in two of our patients who had no evidence for bilateral MT dysfunction, even when both memory criteria and the electrographic criteria were combined. Furthermore, even in some patients with bilateral MT dysfunction on all tests, like our patient 2, unilateral ictal involvement of MT structures may not be sufficient to produce PAS. In patient 2 anterograde amnesia resulted only from ictal involvement of both MT structures. One can also argue that in her case the amnesia for items presented during the initial unilateral phase of the seizure induced by amygdaloid stimulation (the only phase that clinically fulfilled the criteria for PAS) was not truly anterograde, for in electrographically identical, but purely unilateral seizures there was no memory loss. Thus in this case the subsequent spread to the contralateral hippocampus must have induced the amnesia which thus comprised a short-span retrograde element covering the initial unilateral phase of the seizure. Nevertheless, our patients' histories showed no evidence for retrograde amnesia extending into the preictal period.

These observations leave one with a pathophysiological dilemma, for most seizures starting in MT structures are known to propagate first to ipsilateral temporal isocortex and only then to contralateral MT structures (Lieb *et al.*, 1986; Spencer *et al.*, 1987;

P. Gloor and V. Salanova, unpublished results). Under such conditions PAS should not occur, because the bilateral involvement of isocortex would result in the classical full-blown pattern of temporal lobe seizures in which amnesia is associated with unresponsiveness and confusion.

We must therefore postulate that PAS can result from the spread of seizure discharge from MT structures on one side to the contralateral ones without isocortical involvement. The observations on our patient 2 are suggestive of this: the seizure induced by left amygdaloid stimulation which involved the left MT structures when it spread to the right initially spread to the right hippocampus only (Fig. 2). In humans the only reasonable anatomical route available for such a spread is the dorsal hippocampal commissure (Amaral *et al.*, 1984; Demeter *et al.*, 1985; P. Gloor and V. Salanova, unpublished results). The corpus callosum could obviously not carry signals selectively originating from or destined to contralateral MT structures, nor could the anterior commissure, since it does not originate from MT structures, including the amygdala to which it, however, projects together with massive projections to contralateral temporal isocortex (Pandya and Rosene, 1985; Demeter *et al.*, 1990). This leaves only the hippocampal commissural system as a candidate system to sustain such a spread. This system has been considered to be vestigial and nonfunctional in humans on the basis of electrophysiological data (Wilson *et al.*, 1987, 1990). However, anatomical studies by one of us (P. Gloor and V. Salanova, unpublished results) have shown that although the ventral hippocampal commissure is indeed vestigial in humans, the dorsal hippocampal commissure is a bundle of considerable bulk and cannot be regarded as vestigial. Studies in nonhuman primates and other mammals show that this commissure interconnects the presubiculum and some adjacent areas of the parahippocampal gyrus on one side with the entorhinal cortex on the other with a few homotopic entorhinal connections also being included (Amaral *et al.*, 1984; Demeter *et al.*, 1985, 1990). This pattern is confirmed by the study of Wilson *et al.* (1987) in spite of their claim that the human hippocampal commissure is nonfunctional, for they recorded a contralateral evoked response in the hippocampal region when they applied paired-pulse stimulation to the presubiculum where most dorsal hippocampal commissure fibres originate. Effective activation of this pathway may thus require repetitive discharge of its parent neurons. Two other routes of contralateral spread theoretically exist but appear unlikely: one to the contralateral septum, a very weak connection in primates, and back up to the hippocampus (Aggleton *et al.*, 1987), the other to the mammillary bodies and back to the hippocampus via the anterior thalamus and cingulate cortex. In this system too contralateral projections are weak (Veazey *et al.*, 1982).

It remains uncertain in how many patients transmission of seizure discharge to contralateral MT structures via the dorsal hippocampal commissure is a necessary prerequisite for the induction of PAS. Such transmission is probably the crucial factor for the occurrence of PAS in patients in whom only unilateral MT dysfunction can be demonstrated by memory testing. In patients in whom such testing reveals bilateral MT damage, we surmise that unilateral seizure discharge may often be sufficent for producing PAS. However, even in these patients residual contralaterally sustained MT dysfunction may at times be sufficient to prevent the occurrence of PAS unless the seizure discharge is transmitted via the dorsal hippocampal commissure as in our patient 2. In any case, our results demonstrate that bilateral MT dysfunction on memory testing increases the likelihood of occurrence of PAS.

Differential diagnosis of PAS

Pure amnestic seizures raise two differential diagnostic problems. One is that with prolonged postictal amnestic states, the other with transient global amnesia (TGA). Although both conditions bear some similarities to PAS and probably reflect disturbances in MT structures, they must and can be distinguished.

Postictal amnestic states follow upon conventional complex partial seizures that may, however, be overlooked because of their mildness (Gallassi *et al.*, 1988; Tassinari *et al.*, 1991). They are characterized by both anterograde and retrograde amnesia.

We observed one such patient who had a flurry of what appeared to be minor temporal lobe seizures clustered at close intervals over a period of 24 h and subsequently presented an amnestic state lasting for several days, during which there was both anterograde and retrograde amnesia, the latter covering a period of more than 1 mth (unpublished observation). In these instances the amnesia is most likely due to a seizure-induced transient excitotoxic damage to vulnerable populations of neurons in the hippocampus (Sloviter, 1989; Gloor, 1991*b*). Prolonged postictal amnesia differs from PAS by the fact that (i) it is preceded by a conventional complex partial seizure or a cluster of them, while in PAS the amnestic event represents the seizure itself, (ii) retrograde amnesia is present, while in PAS there is none that can be elicited by history, and (iii) there is a longer duration of the amnestic state than is seen in PAS.

The other differential diagnosis to be considered is TGA (Fisher and Adams, 1964; Hodges and Ward, 1989; Hodges and Warlow, 1990). Episodes of TGA do resemble PAS, particularly with regard to the selective impairment of memory function coupled with the preservation of other cognitive abilities. However, the two conditions differ in other respects. (i) Amnestic episodes are the only manifestations in patients with TGA and are usually single or recur only rarely, while PAS are never the only episodic behavioural manifestation, since all patients with PAS also have unmistakable conventional complex partial seizures. Clinical and EEG evidence for an epileptic disorder is thus lacking in patients with unequivocal TGA, although there are allegedly a few exceptions to this (Hodges and Ward, 1989; Hodges and Warlow, 1990). (ii) TGA lasts for one to several hours, while PAS like other complex partial seizures, usually lasts at the most a few minutes. (iii) Anxiety and repetitive questioning is common in patients in the throes of a TGA episode. The patient is thus aware during the episode that there is something wrong with him. By contrast patients with PAS are not aware that there is anything wrong with them *during* the attack; they become aware of this only *after* the event and only because they can draw inferences from some circumstances that there must have been a gap in their capacity to record memories. If circumstances that allow such inferences to be drawn are not present, the patient may remain permanently unaware that he/she had suffered a PAS (*see* our patient 1). (iv) Patients exhibiting episodes of TGA are of middle age or older, whereas patients with PAS are found across all ages like other patients with temporal lobe epilepsy. (v) There is almost always some retrograde amnesia in TGA which is usually not demonstrable in PAS; even during the seizure itself retrograde memory function may be intact. (vi) TGA patients appear severely amnestic to observers, whereas this is not the case for patients subject to PAS.

It is probable that this difference can be explained by the different time course of the two events: it is much easier for an observer to realize that a subject is amnestic if such a state lasts longer than at the most a few minutes as in PAS.

The structures involved in TGA are probably the same as those in PAS, but the mechanism of TGA is unknown, although probably vascular or circulatory (Müller, 1989; Stillhard *et al.*, 1990) and not epileptic as in PAS. Strong evidence for the role of transient hypoperfusion in the territory of the posterior cerebral artery including the hippocampus has been obtained in a recent single photon emission computerized tomography (SPECT) study carried out in a patient during an episode of TGA (Tanabe *et al.*, 1991).

There are, however, a few instances in which a clear differential diagnosis, between TGA and PAS or a prolonged postictal amnesia is difficult to make (Pritchard *et al.*, 1985; Gallassi *et al.*, 1988; Hodges and Ward, 1989; Hodges and Warlow, 1990; Stracciari *et al.*, 1990). Sometimes this is in part due to insufficient clinical information. While some of these episodes may represent PAS, such as the two cases reported by Pritchard *et al.* (1985), others are probably instances of prolonged postictal amnesia, when repeated ictal events, because they were minor and thus devoid of any convulsive phenomena, were missed or assumed to be unimportant (Gallassi *et al.*, 1988; Stracciari *et al.*, 1990.; Tassinari *et al.*, 1991). In cases initially presenting as TGA, the combination of a short duration of the attacks and a recurrence of the episodes is highly suggestive of epilepsy (Hodges and Warlow, 1990).

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EPILEPTIC SEIZURES IN AN ANDEAN REGION OF ECUADOR

INCIDENCE AND PREVALENCE AND REGIONAL VARIATION

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SUMMARY

A large-scale neuro-epidemiological study was carried out in a population of 72 121 inhabitants of a region of Northern Ecuadorian Andean Sierra, to identify prevalence and incidence rates of epileptic seizures and to identify demographic and geographic variations in these rates. Calculations were made using three data sets. First, rates were calculated from all cases identified in the field (raw dataset); secondly, lower rates were calculated based on a further diagnostic and reclassification procedure (minimum estimated dataset); thirdly, higher rates were derived by calculating false negative rates from the screening procedures, and adding these to the cases actually identified (maximum estimated dataset). Lifetime point-prevalence rates between 12.2/1000 and 19.5/1000 were recorded (minimum and maximum estimated rates), and the prevalence of active epileptic seizures was between 6.7/1000 and 8.0/1000 (minimum estimated and raw datasets). Incidence rate ranging between 122/100000/year and 190/100000/year were found (minimum, estimated and raw datasets). A marked difference in prevalence rates was found in two subregions of the survey area, and also in urban and rural areas. The reasons for these differences were not identified.

INTRODUCTION

To formulate rational health policies and to plan adequate medical provisions it is necessary to know the dynamics of disease processes. Most neuro-epidemiological data, and particularly those of epilepsy, come from studies carried out in developed countries; the methodologies of such studies are well tried. There may, however, be significant differences in the characteristics of a condition such as epilepsy in developing countries, for instance in regard to frequency, aetiology, clinical phenomenology, which render the extrapolation of findings from developed societies unreliable. Furthermore, large-scale neuro-epidemiological studies in developing countries will require different methodological approaches, which are much less well established. Design problems exist particularly in regard to case ascertainment and diagnosis (Schoenberg, 1982; Sander and Shorvon, 1987; Shorvon and Farmer, 1988). In the absence of good medical records or research registers, community-based surveys of whole populations are necessary for accurate case ascertainment, requiring specific and sensitive screening instruments and considerable logistical support (Schoenberg, 1982). The diagnosis of epileptic seizures is essentially clinical, and thus does not require sophisticated technology,

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e.g. electroencephalography (EEG); however, it is reliable only if diagnostic criteria are stringently standardized and reproducible. The importance of validation of a screening procedure is a further aspect of neuro-epidemiology which is often overlooked, and yet is crucial to the accurate determination of incidence and prevalence rates (Placencia *et al.*, 1992).

This report is of a large-scale survey of the incidence and prevalence of epileptic seizures in a highland region of Ecuador, in which particular emphasis has been placed on methodological aspects. The detailed design of the study, including aspects of case ascertainment and diagnosis, and the validation of the screening instruments, are published elsewhere (Placencia *et al.*, 1992*a*,*b*). Here, we describe the findings with regard to incidence rates, point-prevalence rates, and lifetime prevalence rates. Overall rates specific for age, sex and geographic subregion are also presented.

MATERIALS AND METHODS

The present study is the epidemiological wing of a large-scale study of epileptic seizures, with the following aims: (i) to identify, directly in the general population of the region, all residents with an history of non-febrile epileptic seizures (cases); (ii) to establish the demographic and epidemiological profile of epileptic seizures in these cases (rates); (iii) to identify regional and demographic variations in these rates; (iv) to assess the suitability of this study design for future neuro-epidemiological studies, in rural areas of developing countries.

Clinical and epidemiological definitions

We used the following definitions:

Epileptic seizure. Epileptic seizures were defined according to clinical protocols and clinical definitions (*see* Placencia *et al.*, 1992*a*), and classified in accordance to the seizure type classification of the International League Against Epilepsy (ILAE) (Commission on Classification and Terminology of the ILAE, 1981), without recourse to EEG data. Included in this study were seizures of all seizure types and aetiologies, including acute symptomatic seizures, and single seizures. Febrile seizures were excluded.

Febrile seizures. Convulsive seizures occurring between the ages of 2 yrs and 5 yrs, in the context of a febrile illness, providing the case had had no more than six seizures in total.

Active epilepsy. Those cases in whom epileptic (non-febrile) seizures had occurred in the 12 mth period prior to the study, and/or who were taking anti-epileptic medication at the time of the study.

Inactive epilepsy. Those cases with a history of non-febrile seizures, in whom no seizures occurred in the 12 mths prior to the study, and who were not taking any anti-epileptic medication.

Incidence. This is defined as the number of cases developing non-febrile epileptic seizures for the first time in the 12 mths prior to inclusion in the study.

Prevalence. This is defined as the number of cases with a history of non-febrile epileptic seizures per 1000 persons in the population. This is a consecutive point-prevalence rate, the consecutive point-dates were from October 22, 1986 to March 10, 1987. Prevalence rates for active and inactive cases are derived.

Lifetime prevalence. Prevalence rates of all cases with a history of non-febrile seizures (e.g. both active and inactive).

Specific rates. Incidence and prevalence rates based on sex and age of onset of the condition, and also according to geographic (urban/rural) distribution.

Study area and population

The study area was chosen because of its ease of access and communication, and because it was considered representative of the whole highland region. The area of about 75000 persons was divided in two geographic subregions; a humid temperate region situated up to 3200 m above sea level, containing about three-quarters of the population, and a dry temperate region situated at about 1500 m above sea level. Of 72121 persons surveyed (97% of the total population), 12768 (18%) lived in an urban setting (one of the three provincial towns in the region) and 59353 (82%) in a rural setting. Most of the population are subsistence farmers. The majority are mestizo of Amerindian and white descent and approximately 12% are black.

The health-care infrastructure in this region consists of 38 rural medical services health centres and two district hospitals, staffed by 40 general physicians and ancillary workers. The nearest town with EEG and computerized tomography (CT) scan resources is Quito, 270 km away.

In the planning stage of the study, the area was divided in 160 sectors based on existing maps which were updated by the study team in the field. Initial predictions concerning the demographic data were based on the 1982 Ecuadorian national census.

Design

This is described in detail elsewhere (Placencia *et al.*, 1991) and is summarized here (*see* Fig. 1).

Step 1. A house-to-house survey was carried out between October 1986 and March 1987, using a screening instrument which had been piloted and validated, with the aim of identifying all persons in the population with a possible history of non-febrile epileptic seizures. The survey was conducted by 54 screening personnel. The screening instrument had a specificity of 92.9%, a sensitivity of 79.3%, an adjusted positive predictive value of 18.3% and negative predictive value of 99.6% (Placencia *et al.*, 1992*b*).

Step. 2. The possible cases identified in step 1 were examined by one of a team of rural doctors, trained in the use of precise operational definitions. Cases were categorized as: epileptic seizures; febrile seizures, uncertain case or false positives.

Step 3. Cases defined as epileptic seizures and all uncertain cases were then seen by one of a team of specialist neurologists, using the same operational definitions. All those confirmed as having afebrile epileptic seizures by the neurologist, were then given a standardized neurological interview and examination to record clinical details.

Step 4. A research case record review of all cases from step 3 was carried out by an international neurological panel. Based on the information available, these cases were further reclassified into definite and probable cases.

Step 5. A random sample of 1.4% of all negatives from the original door-to-door screening (step 1) were interviewed by one of the rural doctor team, to ascertain the false negative rate from step 1.

Step 6. A random sample of 4.6% of the false positives from step 2 were examined by one of a team of specialist neurologists. This was to identify the false negative rate from step 2.

Step 7. To assess inter-observer reliability of the neurological diagnosis, a sample of 349 (33.9%) cases was re-examined with strict clinical criteria.

The screeners (step 1) were secondary school-leavers who received basic training. The rural doctors (steps 2 and 5) were recently qualified doctors, carrying out an obligatory 1 yr pre-registration tour in rural medicine. Eleven of them participated in the study and they were given a 5 d *ad hoc* course to familiarize themselves with the diagnostic process. One of a team of 12 senior neurologists, from the Ecuadorian Society of Neurology carried out the final field examination (steps 3 and 6), which acted as the diagnostic gold standard for the field identification of cases. The international panel (step 4) consisted of neurologists with a special training in epilepsy. There was always a neurologist in the study area and they all participated in standardization workshops with the investigators. One epidemiologist based in Quito collaborated in the planning and the cartographic aspects. Five rural physicians were trained to coordinate the fieldwork. The principal investigator lived in the study area for the duration of the study.

Data were entered in the field into floppy diskettes using the DataEase (DataEase International) software package. The analysis was carried out partly in London and partly in Quito (*see* Placencia *et al.*, 1992*a* for details).

Datasets used for the calculation of rates

Calculations of incidence rates were made in two specific datasets (A, B) and calculation of prevalence rates were made on three specific datasets (A, B, C):

A. Raw dataset (1029 cases). This comprises all cases identified by the neurologists in the field in step 3.

B. Minimum estimated dataset (881 cases). This comprises those cases confirmed as definite epilepsy following the records review of cases (step 4). This recalculation excludes any case in which diagnostic information was not sufficiently comprehensive. This procedure undoubtedly excludes some cases of epilepsy

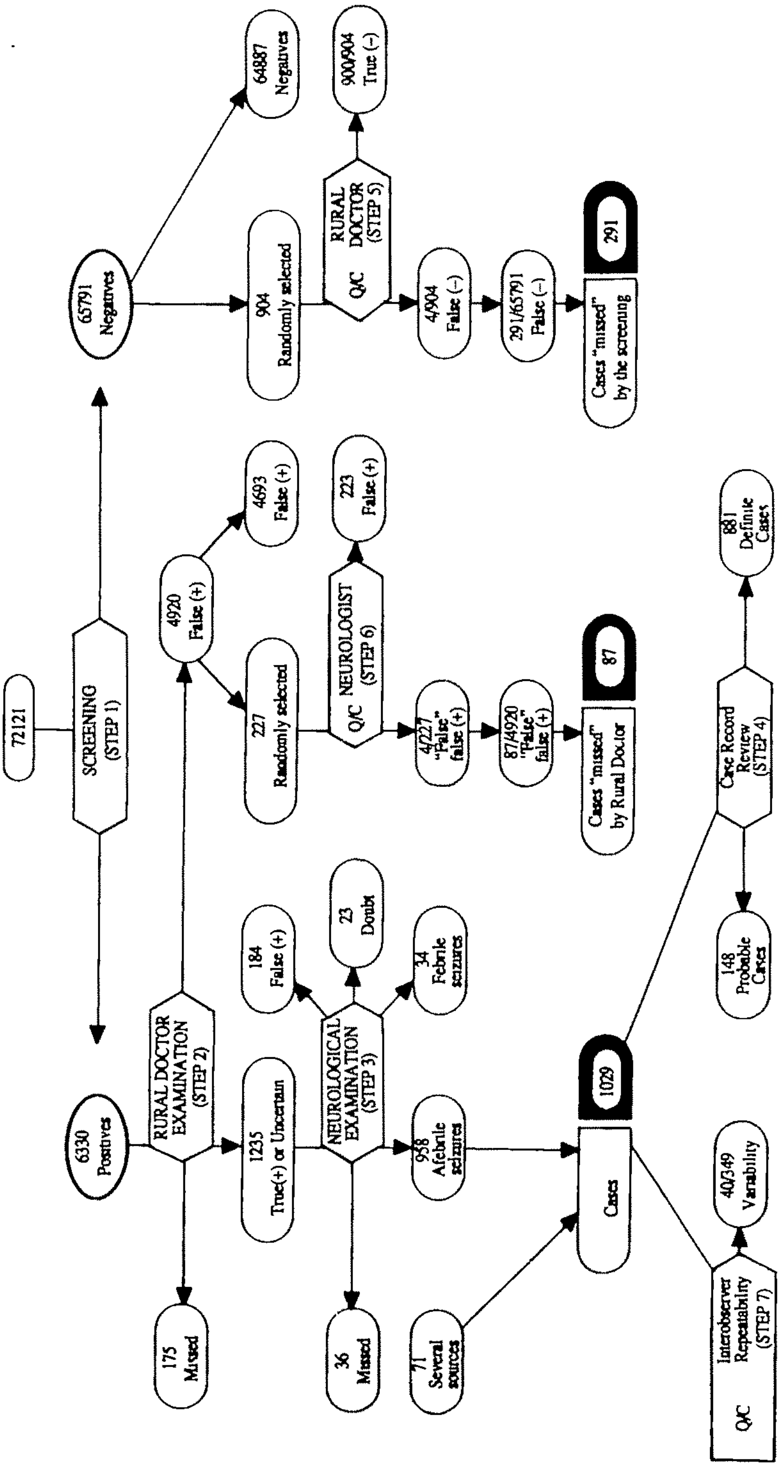
72121
SCREENING (STEP 1)
6330 Positives
65791 Negatives
RURAL DOCTOR EXAMINATION (STEP 2)
175 Missed
1235 True(+) or Uncertain
4920 False (+)
4693 False (+)
227 Randomly selected
Q/C NEUROLOGIST (STEP 6)
223 False (+)
4/227 "False" false (+)
87/4920 "False" false (+)
Cases "missed" by Rural Doctor
87
64887 Negatives
904 Randomly selected
Q/C RURAL DOCTOR (STEP 5)
900/904 True (−)
4/904 False (−)
291/65791 False (−)
Cases "missed" by the screening
291
NEUROLOGICAL EXAMINATION (STEP 3)
184 False (+)
23 Doubt
34 Febrile seizures
36 Missed
958 Afebrile seizures
71 Several sources
Cases
1029
Case Record Review (STEP 4)
148 Probable Cases
881 Definite Cases
Q/C Interobserver Repeatability (STEP 7)
40/349 Variability

FIG 1

identified in the field but in whom some data are absent or unclear. For instance, those cases where witnessed accounts were missing, or where seizures occurred in the past, or were infrequent, or where there was doubt about seizure details. This calculation was made to ensure that a group of cases was isolated, in whom data were comprehensive. It also reflects the inevitable diagnostic uncertainty that exists in epilepsy (and indeed in other conditions where diagnosis is based on clinical history).

C. Maximum estimated dataset (1407 cases). This comprises all cases from the raw dataset and an additional estimated number of cases, assumed to have been missed on screening (calculated from the false negative rate of the screening procedure identified in the validation of the screening procedure, steps 5 and 6).

All three datasets are used for overall prevalence figures. The minimum estimated and raw datasets are used for calculations of the incidence rates and prevalence rates for active and inactive cases. The raw dataset is used for calculations of regional variations and of the age and sex specific prevalence rates.

RESULTS

In Table 1 is shown the sex and age distribution for the total sample (i.e. the 72 121 persons screened). This represents 97% of the total estimated population of the region.

Step 1. Of the 72 121 persons, 65 791 were found to be negatives and the remaining 6330 (8.8%) were positive.

Step 2. Of the 6330 positives, 6155 (97%) were examined by a rural doctor. Of these, 1235 were considered to be cases of epileptic seizures or probable cases.

Step 3. The neurologists interviewed 1199 (97%) of the 1235 cases identified by the rural doctor. They confirmed 958 as true positives, 34 as febrile convulsions only, 184 as false positives and the remaining 23 cases as probable. In addition, the neurologist also confirmed a history of non-febrile seizures in another 71 cases, who had incomplete documentation from the previous stages. Of these 38 were positive at the screening, but were not seen by the rural doctor, and 33 were cases about whom the rural doctor had some diagnostic query. Therefore, the neurologist diagnosed 1029 cases of afebrile seizures (958+71).

Step 4. The review of the 1029 research case records reclassified 881 as definite cases and 148 as probable cases.

Step 5. Of a random sample of 1.37% of the screened negatives, i.e. 904 of 65 791, four (0.44%) were found to be positives missed in the door-to-door screening. If this proportion is projected to all negative cases, a further 291 false negatives could be expected.

Step 6. Neurologists examined a random sample of 4.6% of the cases classified as false positive by the rural doctors (i.e. 227 of 4920) and identified four cases (1.76% of 227) as positive. If this proportion is projected to all rural doctor false positive cases, a further 87 cases could be expected.

TABLE 1 AGE AND SEX DISTRIBUTION OF THE POPULATION SCREENED

	Age in years								
	0–9	*10–19*	*20–29*	*30–39*	*40–49*	*50–59*	*60–69*	*70–98*	*Total*
Males	10 007	9409	4638	3315	3015	2390	1563	1427	35 827
Females	10 001	8856	4790	3842	3237	2568	1612	1388	36 294
Total	20 071	18 265	9428	7157	6252	4958	3175	2815	72 121
Percentage rate	27.8	25.3	13.1	9.9	8.7	6.9	4.4	3.9	100.0

Step 7. In 11.5% of the 349 cases selected for the inter-observer reliability assessment, the diagnosis of epileptic seizures was questioned and this will be discussed elsewhere.

Another possible source for missing cases would be those positive at screening but who were not seen by a doctor. Of these, 28 would be expected to be confirmed as positive cases (assuming that the same relative proportion of confirmed cases from screen positive cases occurred in the main populations applied). Similarly, we would expect 29 additional cases from the other 36 subjects who were not seen by the neurologist (Fig. 1). These 57 (28+29) possibly missed cases will not be taken further into account as they refused examination and may not be comparable to the general group.

Prevalence and Incidence rates

(i) The minimum lifetime prevalence in the population is 12.2/1000 (881/72 121, dataset *B*).
(ii) The maximum lifetime prevalence is 19.5/1000 (1407/72 121, dataset *C*).
(iii) The prevalence of active cases ranges between 6.7/1000 to 8.0/1000 and lifetime prevalence from 12.2/1000 to 14.3/1000 (from datasets *B* and *A*).
(iv) The annual incidence rates range from a minimum estimate of 122/100 000 to a maximum 190/1 000 000 (from datasets *B* and *A*).
(v) Sex and age specific rates are shown in Table 2 (from dataset *A*).
(vi) Lifetime prevalence rates specific for the two subregions and for urban and rural cases within each region are shown in Table 3 (from dataset *A*).
(vii) The seizure types of all cases from datasets *A* and *B* are shown in Table 4.

TABLE 2 SUMMARY OF EPIDEMIOLOGICAL FINDINGS

	Age in years								
	0–9	*10–19*	*20–29*	*30–39*	*40–49*	*50–59*	*60–69*	*70–98*	*Total*
Incidence (per 100 000 per year)									
Males (n)	13	32	4	3	5	2	1	2	62
Females (n)	22	17	13	1	11	5	3	3	75
Total (n)	35	49	17	4	16	7	4	5	137
Percentage rate	174.4	268.3	180.3	55.9	255.9	141.2	126.0	177.6	190.0
Prevalence (active cases) (per 1000)									
Males (n)	30	76	40	30	25	23	5	9	238
Females (n)	44	72	54	45	57	35	16	14	337
Total (n)	74	148	94	75	82	58	21	23	575
Percentage rate	3.7	8.1	10.0	10.5	13.1	11.7	6.6	8.2	8.0
Lifetime prevalence (per 1000)									
Males (n)	69	138	60	51	45	38	17	16	434
Females (n)	79	116	85	90	99	67	35	24	595
Total (n)	148	254	145	141	144	105	52	40	1029
Percentage rate	7.4	13.9	15.4	19.7	23.0	21.2	16.4	14.2	14.3
Age of onset of epilepsy (no. of patients with onset by decade)									
Males (n)	161	128	54	37	24	21	6	3	434
Females (n)	174	177	101	57	46	24	10	6	595
Total (n)	335	305	155	94	70	45	16	9	1029

(n) = number of cases. All rates calculated from the raw dataset values and the population basis (Table 1)

TABLE 3 DISTRIBUTION OF LIFETIME PREVALENCE RATE (PER 1000), BY GEOGRAPHIC SUBREGIONS AND FOR URBAN/RURAL POPULATION (RAW DATASET)

Subregion	*N*	*n*	*Percentage rate*
Region I			
Urban	10 667	81	7.6
Rural	45 068	541	12.0
Subtotal	55 735	622	11.2
Region II			
Urban	2101	35	16.7
Rural	14 285	372	26.0
Subtotal	16 386	407	24.8
Whole area (I+II)			
Urban	12 768	116	9.1
Rural	59 353	913	15.4
Total	72 121	1029	14.3

N = population at risk; n = number of cases.

TABLE 4 SEIZURES CLASSIFICATION, FOR BOTH RAW AND MINIMUM ESTIMATED DATASET

	Raw dataset[1]		*Minimum estimated dataset*[2]	
Seizure type	*n*	*Percentage*	*n*	*Percentage*
Partial	468	46	437	49
Simple	95	9	17	2
Complex	54	5	44	5
Secondary generalization	319	31	298	34
Partial with secondary generalization	–	–	78	9
Generalized	539	52	430	49
Tonic clonic	443	43	378	43
Other generalized[3]	96	9	25	3
More than one type of generalized seizure	–	–	27	3
Unclassifiable	22	2	14	2
Total	1029		881	

[1] Based on main seizure type only, [2] based on all seizure types (in patients with more than one seizure type), [3] atonic, absences and myoclonic seizures.

DISCUSSION

Epidemiological studies in the developing world require methodological approaches different from those in developed countries. This is because of the relative absence of accurate case registers or medical records, the lack of sophisticated technology and because specialist trained medical staff are usually concentrated in the larger towns. The design of this current study deliberately address these issues and certain features are worth emphasis. First, case ascertainment was achieved by a house-to-house survey of the entire population, which did not rely on existing medical records or previous medical contact. The potential logistical difficulties which such a large-scale study might raise were circumvented by the use of a cascade system for diagnostic confirmation. Cases were first screened by non-medical personnel, then examined by rural doctors, then by specialized neurologists and finally reviewed by an international panel. This cascade system allowed the input of specialists to be focused and therefore their efficiency maximized. The screening instruments and procedure were piloted and validated, and quality control exercises were undertaken at each stage of the screening process to identify false negative rates (*see* Placencia *et al.*, 1992*a*,*b* for further details of the methodology and validation of the study). The diagnosis of epileptic seizure was carried out according to stringent standardized clinical algorithms, and as such was reliable and reproducible. Non-specialist initial screening depends on the ease of use of the clinical protocols: and in the current study, these were highly successful. These aspects are emphasized, as they are important features of any such neuro-epidemiological investigation in the setting of a developing country.

A principal aim of this wing of the study, was to identify prevalence and incidence figures. We have deliberately chosen to calculate these neuro-epidemiological values from three different datasets, and thus to present the rates in the form of a range rather than as single figures. The basic figures are derived from the numbers of cases identified by the neurologists in the field (1029 cases; dataset *A*: step 3). A minimum rate is derived from a review of the records of all these cases in which diagnosis and classification was subjected to stringent clinical review (881 cases; dataset *B*: step 4) to identify cases where data were comprehensive. This undoubtedly lead to the exclusion both of some cases of epilepsy but also of others where the diagnosis could be incorrect. This procedure was carried out in order to arrive at a dataset, in which data were comprehensive and were undertaken in the recognition (uncomfortable as this is for epidemiologists) that there exists a group of cases in whom the diagnosis of seizure cannot be made with certainty, a problem with all conditions in which diagnosis is based on clinical history. The issue was further explored by seeking to identify inter-reliability rate between observers, and we found a possible variation of 11.5% in a sample of 349 cases. This is a further demonstration of the fact that epileptic seizures are essentially a clinical diagnosis, at the fringe of which are cases where clinical opinions differ; some cases were conceivably pseudoseizures or faints, and both diagnoses pose a common clinical problem in epilepsy practice. This diagnostic grey area has been ignored in previous epidemiological studies, yet we feel it is an important factor when presenting epidemiological findings. It is to reflect this element of diagnosis uncertainty that we have expressed our data as a range rather than a single number. A maximum rate was calculated from the raw data, adjusted upwards by the addition of a projected number of cases, assumed to have been missed out by the screening procedures (1407 cases; dataset *C*: steps 5 and 6). Such calculations provide a range of figures which has more validity than a single raw figure, and reflects the realities of a large-scale screening exercise of a condition of which the diagnosis is based on clinical data. Again, we emphasize these aspects, as they are important issues for the design of future neuro-epidemiological studies of epileptic seizures.

The incidence rate identified in the study was based on 12 mths retrospective data. A similar method was used in a smaller study in the Andean region carried out in 1984 (Placencia *et al.*, 1984), and by Li *et al.* (1985) in China. The incidence rate is higher than is often quoted, and we feel reflects the comprehensive nature of the case ascertainment. In the previous Andean study an overall incidence rate of epilepsy of 230/100 000/year was found, which is comparable with that of 190/100 000/year found in this study. There was no striking effect of sex on the incidence rates, confirming findings from other studies. However, fewer cases than expected had seizure onset in the first decade. The relevance of this is uncertain; one possible explanation is that the screening procedures were less satisfactory in children. The actual number of cases is relatively small, and confidence limits are large, hence firm conclusions cannot be drawn.

Prevalence rates are much higher than incidence rates in chronic condition such as epilepsy, so studies of prevalence have been carried out much more frequently. We have reviewed the results of a number of epidemiological studies from various parts of the world, carried out between 1960 and 1989. In 48 of these studies, details either of the proportion of active cases or of the age range of the population at risk were given (Pond *et al.*, 1960; Krohn, 1961; Levy *et al.*, 1964; Sato, 1964; Aall-Jilek, 1965; Gudmundsson, 1966; Wajsbort *et al.*, 1967; Leibowitz and Alter, 1968; Mathai *et al.*, 1968; Dada, 1970; Giel, 1970; Olivares, 1972; Poskanzer, 1972; Stanhope *et al.*, 1972; Rose *et al.*, 1973; de Graaf, 1974; Zielinski, 1974; Hauser and Kurland, 1975; Meighan *et al.*, 1976; Rowan and Hyman, 1976; Baumann *et al.*, 1977, 1978; Gomez *et al.*, 1978; Chiofalo *et al.*, 1979; Cavazzuti, 1980; Gutierrez *et al.*, 1980, 1983; Pascual *et al.*, 1980; Beran *et al.*, 1982; Osuntokun *et al.*, 1982; Garcia-Pedroza *et al.*, 1983; Goodridge and Shorvon, 1983; Goudsmit *et al.*, 1983; Granieri *et al.*, 1983; Cruz *et al.*, 1984; Placencia *et al.*, 1984; Pradilla *et al.*, 1984; Ponce *et al.*, 1985; Carpio *et al.*, 1986; Haerer *et al.*, 1986; Joensen, 1986; Marino *et al.*, 1987; Osuntokun *et al.*, 1987; Bharucha *et al.*, 1988; Koul *et al.*, 1988; Tsuboi, 1988; Zuloaga *et al.*, 1988; Chiofalo *et al.*, 1989; Cowan *et al.*, 1989; Hernandez *et al.*, 1989). The average prevalence rates reported in these studies is 18.5/1000 (range 2.8–44/1000) for children and 10.3/1000 (range 1.5–37/1000) for all ages. These studies have varying methods and definitions, are of differing size and sophistication and come from many differing countries. Nevertheless they provide a background against which to assess the current findings. Most studies from developing countries report higher prevalence than those from developed countries and higher rates amongst children, although there is considerable overlap in the range of findings reported. The prevalence findings in our own study are similar to those reported elsewhere in the developing world, although the high prevalence amongst young patients reported in some other studies is not so clearly seen. The definition used for active cases in our study (i.e. a seizure in the previous year, and/or on anti-epileptic medication) is more restrictive than in other studies, and the emphasis is placed on an unselected community-based population, avoiding selection bias, which is often introduced in less methodologically stringent studies; both these factors may influence prevalence rates, and comparisons between studies using differing designs and definitions may be difficult.

An important finding is the variation in rates in the two study regions (lifetime prevalence of 11.2/1000 in region 1, and 24.8/1000 in region 2). This difference occurred in spite of identical methods and design, the application of similar protocols and study design, and diagnostic conformation by the same team of neurologists. Thus, this is not likely to be artefactual or attributable to differences in methods, but to represent a real geographic variation. Similar geographic variations in contiguous regions have not been previously reported. We also considered the possibility that these observed differences were attributable to differential rates in urban and rural settings. As shown in Table 3, however, although the prevalence of epilepsy was higher in rural than in urban surroundings in both regions (prevalence rates are 15.4/1000 and 9.1/1000), the difference was not sufficient to account for the regional variation. A higher incidence of epilepsy in rural populations has also been noted in a previous ICBERG study in Turkey (A. Gouvenor, personal communications), although only these two studies had directly compared rural and urban regions. However, no clear aetiological reasons for these differences were identified. These differences are of great potential importance, for herein may lie a clue to the aetiology of epilepsy, in Ecuador and beyond, and indeed possibly provide a basis for the prevention of epilepsy. Future neuro-epidemiological work should be carried out to identify the reasons for these marked differences.

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VALIDATION OF A SCREENING QUESTIONNAIRE FOR THE DETECTION OF EPILEPTIC SEIZURES IN EPIDEMIOLOGICAL STUDIES

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SUMMARY

A large-scale clinico-epidemiological study of epileptic seizures has been carried out in a highland area in northern Ecuador, South America. This paper describes the design and the two-staged validation procedures undertaken to authenticate the screening questionnaire, which was used to detect epileptic seizures in the community during this project. An initial questionnaire consisting of 20 questions was devised and then validated in a group of healthy subjects and a group of patients with known epileptic seizures. This questionnaire was found to have a sensitivity of 100% and a specificity of 50.8%. A cluster analysis of the responses rates was undertaken and a set of nine questions which presented a specificity of 92% and sensitivity of 98% were chosen to be used during the survey. The validation of this nine-question instrument was then undertaken by direct application to a general population of 72 121 persons. Positive, negative, false positive and false negative rates were derived. The screening instrument was found to have a sensitivity of 79.3%, a specificity of 92.9%, a positive predictive value of 18.3%, a negative predictive value of 99.6% and a Youden's index of 0.79. The methodology of the study and the instruments developed are recommended for future neuro-epidemiological work in epilepsy. The problems of validation are discussed, and previous epidemiological studies of epilepsy reviewed with special emphasis on the handling of questions of validation.

INTRODUCTION

It has been common practice during the last three decades, for epidemiologists to use a two-staged approach for the identification of cases of a given condition in the community (Mausner and Bahn, 1977). The first step is the application of simplified interviews or screening techniques to identify suspected cases; the procedure can be a simple laboratory test (e.g. blood sugar estimations for diabetes) or a screening questionnaire. This step is designed to be simple, inexpensive and require no sophisticated facilities. The efficacy of this screening procedure depends on the sensitivity and specificity of the screening instrument. The second step involves a specialist examination of all the suspected cases identified by the previous screening. Cases are then categorized into *true positives* or *false positives*. Here sophisticated diagnostic resources may be needed. In the majority of epidemiological studies, however, the second step is a simple clinical examination; a perfectly appropriate procedure in epilepsy, which is defined by clinical criteria, and is an entirely clinical diagnosis.

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Methodological problems of epidemiological studies of epilepsy have been extensively reviewed (Alter *et al.*, 1972; Robb, 1972; Rose *et al.*, 1973; Zielinski, 1974; Hauser and Kurland, 1975; Baumann, 1982; Schoenberg, 1982*a*,*b*; Haerer *et al.*, 1986; Sander and Shorvon, 1987; Shorvon and Farmer, 1988). Interest has generally centred on case ascertainment, classification and definitions but to date the issues regarding the validity of the screening instruments have not been fully discussed. In response to a screening questionnaire, populations under study are grouped into possible cases (*positives*) and into apparently healthy persons (*negatives*). If the sensitivity of the screening instrument is low, many *false negatives* will be missed in the community. On the other hand, if the screening questionnaire has a low specificity, a large number of *false positives* will be included as possible cases, generating serious logistical difficulties for stage two. Thus, the effectiveness of the screening questionnaire is of critical importance to the design of any epidemiological study.

Validation is the process of establishing the degree of accuracy of an instrument. MacMahon and Pugh (1981) state that validation is the procedure to assess the ability of an instrument to recognize observations which apply to real situations, established simultaneously by more accurate and precise methods. Two measures of importance are usually quoted; the sensitivity and specificity (Mausner and Bahn, 1977; Lilienfeld and Lilienfeld, 1980; MacMahon and Pugh, 1981; Rumeau-Rouquette *et al.*, 1981; Schoenberg, 1982*c*). The sensitivity of an instrument is a measure of its ability to distinguish as positive those subjects who have the condition under investigation (i.e. low false negative rates). Specificity is a measure of the ability to correctly identify those subjects who do not have the condition (i.e. low false positive rates). The sensitivity of a test is defined as the number of true positives correctly identified by the test, divided by the sum of the true positives and false negatives (×100). The specificity is defined as the number of true negatives correctly identified by the test, divided by the sum of the false positive and true negatives (×100). In addition, the predictive value originally described by Vecchio (1966) is a useful measure in a validation process, which accounts for the prevalence of the condition as well as the specificity and sensitivity of the instrument. The positive predictive value of an instrument is the proportion of subjects who are positive and have the condition under investigation (the number of true positive cases divided by the sum of the numbers of true and false positives ×100). The negative predictive value is the proportion of subjects who are negative and do not have the condition (the number of true negatives divided by the sum of the numbers of true and false negatives ×100). Also useful is an Youden's index (Armitage and Berry, 1987) which is an estimate of the diagnostic value of the instrument; the diagnostic value is greater, the nearer to unity is the index (derived by the subtraction of the probabilities of false positives and false negatives from unity).

Validation procedures can be undertaken in two different settings. In the first, two selected samples of subjects who are known to have the condition (cases) and who are healthy (non-cases) are chosen, to whom the instrument under study is applied. The positive and negative rates on screening are then compared with the previously known diagnostic status. This method is effective as data for both healthy persons and cases can be gathered. However, generalization of results is limited by the selection criteria and by the fact that it is carried out in an artificial setting. The power of the method depends on the size of the sample and the level of diagnostic sophistication; cost and logistical difficulties may limit these. We shall call this method the *clinic-based validation*.

The second method to validate an instrument is to derive rates directly from its application to a general population. Generalization of findings from this approach are more powerful as they are obtained in a less artificial setting. The main limitation of the method, however, is that it is not usually possible to apply to an accurate diagnostic examination to the whole population being studied due to the high cost of such an exercise. A sample of the population must be examined for validation purposes, and the results extrapolated to the whole population. Data therefore are partly indirect. We have called this method the *field validation*.

Between 1986 and 1987, a large-scale clinico-epidemiological study of epileptic seizures was carried out in a highland area in northern Ecuador, South America, the methodology of which is described in detail elsewhere (Placencia *et al.*, 1991) and is summarized in the following paper. In order to undertake this study, it was imperative to have a screening questionnaire capable of being used in large communities which had a better sensitivity and a higher specificity than existing instruments. In this paper details of the design and of the validation procedures undertaken to authenticate this screening questionnaire are presented. Both clinic-based and field validation were carried out.

CLINIC BASED VALIDATION

Material and methods

A screening instrument of 20 questions was designed, based on the authors' clinical experience (Appendix 1). The screening questionnaire was designed to identify patients with a history of epileptic seizures. An affirmative answer to any of the questions would identify the subject as a *positive* case.

In developed countries where the majority of the population is registered under a health system it is, theoretically at least, relatively easy to choose a homogeneous and comparable group of patients with the same diagnosis and simultaneously select a group of people without the condition under study and apply a screening instrument. In developing countries, such as Ecuador, where medical records are less comprehensive, healthy subjects usually will have to be identified in the community. We employed a strategy utilized previously in another survey carried out locally (Placencia *et al.*, 1984), in which the validation sample was formed from two different sources. First, healthy subjects were identified from a survey in a village. Secondly, known patients with epilepsy, with a matched socio-cultural background, were selected from three hospital clinics in Quito (Hospital Andrade Marin run by the Ecuadorian Institute of Social Security was a source for adult patients, Hospital Eugenio Espejo, a Ministry of Public Health establishment was a source for adult and paediatric patients, and Hospital Baca Ortiz, also run by the Ministry of Public Health was a source for children).

Screening was carried out by six high school-leavers, none of whom was a health worker or professional surveyor. They underwent a short training course to accomplish a high level of uniformity. The reference diagnosticians were three consultant neurologists, all of whom had previously attended the training course. A specially prepared diagnostic protocol (algorithm) was used. Diagnosis was always undertaken on clinical grounds, according to stringent clinical criteria, and in the hospital cases with hospital notes.

Results

Table 1 shows the sex and age distribution by years of the healthy controls (no seizures) and patients (cases with seizures). Fifty-five of the 87 patients had partial seizures (six simple partial, 16 complex partial alone, and 33 partial with secondarily generalization). Thirty of the patients had generalized seizures (17 tonic clonic, five other generalized and eight mixed generalized seizures).

Of the 63 controls, 32 were screened as negative and 31 positive, and of the 87 patients, all were positive on screening; a sensitivity of 100% and a specificity of 50.8%. In order to improve specificity (and maintain the high sensitivity), a cluster analysis of the responses rates was undertaken, and a set of nine questions

TABLE 1 AGE AND SEX DISTRIBUTION OF THE CLINIC-BASED VALIDATION GROUP

	Males		*Females*		*Total*			
Age in years	*Patients*	*Controls*	*Patients*	*Controls*	*Patients*	*Controls*	*Total*	*Percentage*
0– 9	18	12	8	11	26	23	49	32.7
10–19	5	5	12	9	17	14	31	20.7
20–29	4	3	7	6	11	9	20	13.3
30–39	8	2	8	5	16	7	23	15.3
40–49	3	1	6	2	9	3	12	8.0
50–59	0	2	2	0	2	2	4	2.7
60–69	2	1	1	2	3	3	6	4.0
>70	3	1	0	1	3	2	5	3.3
Total	43	27	44	36	87	63	150	100.0

were chosen which had a combination of specificity (92%) and sensitivity (98%) (on screening, of the 63 controls, five were positive and 58 negative; and of the 87 patients, 85 were positive and two were negative). No questions that would readily identify absences or myoclonic seizures were included in the final nine questions, but this combination was felt acceptable for general screening purposes. The questionnaire is shown in Appendix 2.

FIELD VALIDATION

Material and methods

The revised questionnaire (nine questions) was then applied to 72 121 people in a door-to-door population survey, undertaken in the highlands of northern Ecuador. This was combined with a demographic instrument. The questionnaire was designed to identify all cases who had suffered epileptic seizures. All seizure types were included, as were single seizures, acute symptomatic seizures. In stage 2, febrile seizures were designed to be excluded by a simple clinical algorithm, although a small number of cases slip through (*see below*). The methodology and definitions used and other details of this study are described elsewhere (Placencia *et al.*, 1992*a*,*b*). The study plan is summarized in Fig. 1.

A cascade system of diagnostic confirmation was used for each case, as follows:

Step 1. Door-to-door survey involving 72 121 people, using the screening medical questionnaire (Appendix 2) and demographic questionnaire.

Step 2. Positive cases were examined by rural doctors, specially trained for the use of the clinico-epidemiological definitions of epileptic seizures (*see* Placencia *et al.*, 1992).

Step 3. Cases considered positive or uncertain by the rural doctors were then examined by specialist neurologists, from the Ecuadorian Society of Neurology.

Step 4. The research case records from the positive cases from step 3 were subjected to an international panel review.

In addition to this, three 'quality control' steps were undertaken, of which two (steps 5 and 6) allowed field validation of the screening instruments:

Step 5. Rural doctor examination of some screening negative cases.

Step 6. Neurologists examination of some rural doctor negative cases.

Step 7. To assesss inter-observer reliability of the neurological diagnosis, a sample of 349 (33.9%) cases was re-examined with strict clinical criteria.

The findings from the seven steps were as follows:

Step 1. Of the 72 121 persons surveyed, 6330 (8.8%) people were positive.

Step 2. One of the 11 rural doctors examined 6155 (97%) and of these 1235 were considered true positives or uncertain.

Step 3. Twelve consultant neurologists then examined 1199 (97%), of whom 958 were confirmed as patients with afebrile seizures and 34 as cases of febrile seizures (these 34 cases slipped through the screening

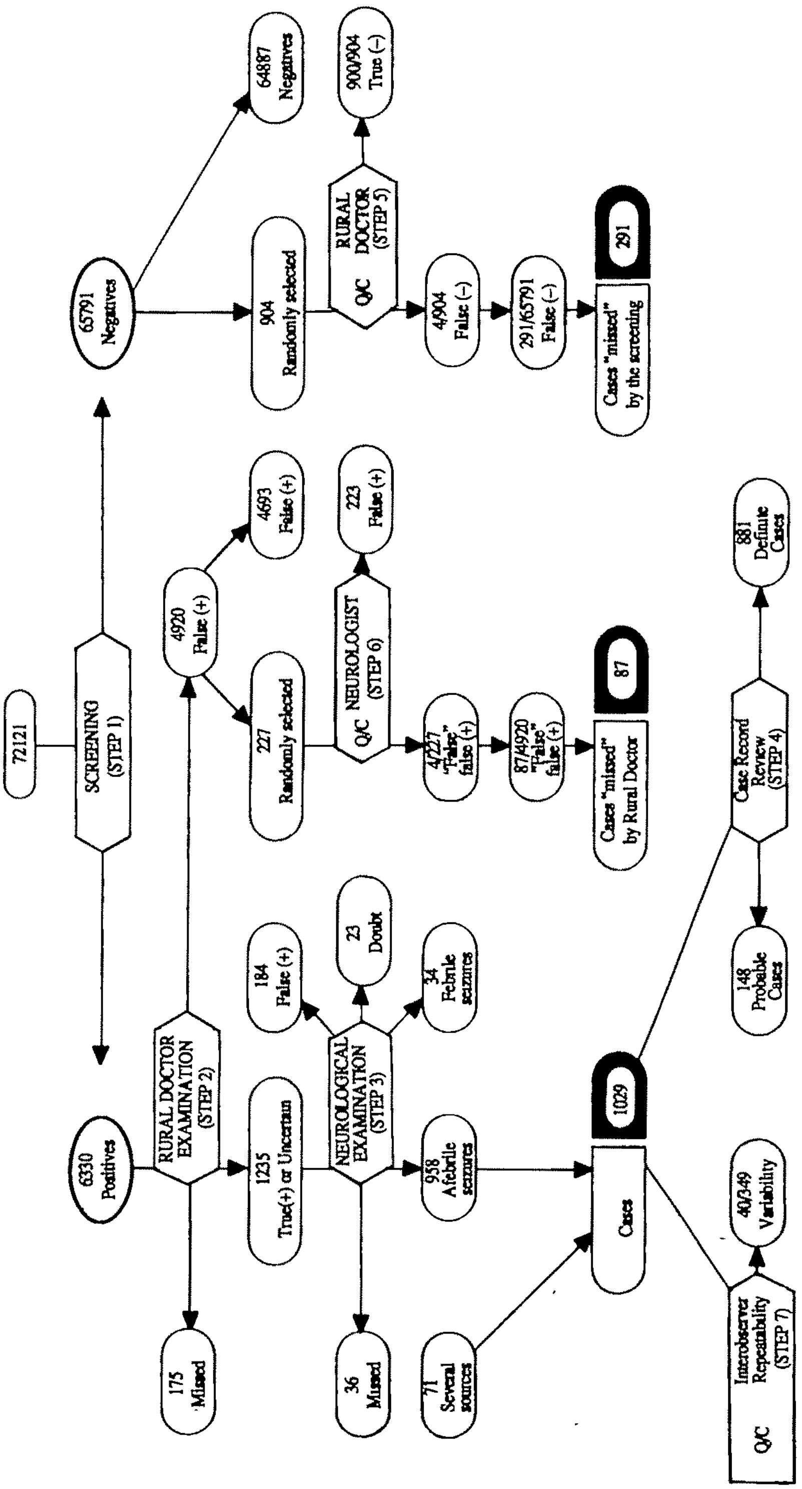
72121
SCREENING (STEP 1)
6330 Positives
65791 Negatives
64887 Negatives
904 Randomly selected
Q/C RURAL DOCTOR (STEP 5)
900/904 True (-)
4/904 False (-)
291/65791 False (-)
Cases "missed" by the screening
291
RURAL DOCTOR EXAMINATION (STEP 2)
175 Missed
1235 True(+) or Uncertain
4920 False (+)
4693 False (+)
227 Randomly selected
Q/C NEUROLOGIST (STEP 6)
223 False (+)
4/227 "False" false (+)
87/4920 "False" false (+)
Cases "missed" by Rural Doctor
87
NEUROLOGICAL EXAMINATION (STEP 3)
36 Missed
184 False (+)
23 Doubt
34 Febrile seizures
958 Afebrile seizures
71 Several sources
Cases
1029
Case Record Review (STEP 4)
881 Definite Cases
148 Probable Cases
Q/C Interobserver Repeatability (STEP 7)
40/349 Variability

FIG. 1

algorithm). Two hundred and seven cases were rejected: 184 as false positives and 23 as uncertain cases. In addition, the neurologists also confirmed a history of afebrile seizures in 71 patients who had incomplete documentation from the previous stages. Thirty-eight were positive at the screening but were not seen by the rural doctor, and in the remaining 33 the screening procedure documentation data were incomplete. Therefore, the neurologists diagnosed 1029 (958+71) cases of afebrile seizures, 996 of whom were screen positive.

Step 4. A research case record review of the 1029 cases (958+71) was carried out, and 881 (85.62%) were considered to be certain (definite) cases, and 148 probable cases.

Step 5. To ascertain false negative rates at screening (defined as people who although having a history of epileptic seizures responded to the screening negatively), a random sample of 904 people (1.37%) out of 65 791 negatives were interviewed by a specially trained rural doctor. Of these four (0.44%) were found to be positive, and these cases were confirmed by a neurologist. If this proportion is projected to the total number of negatives (65 791), a total of 291 false negatives would be expected.

Step 6. Two hundred and twenty-seven (4.61%) people out of the 4920 deemed as false positives (defined as those without epilepsy who responded positively to screening) by the rural doctors were examined by the neurologists. Four (1.76%) were found to have a history of epileptic seizures, and if this proportion is projected to the total (4930), a further 87 cases should be expected.

Step 7. In 11.5% of the 349 cases selected for the inter-observer reliability assessment, the diagnosis of epileptic seizures was questioned.

The numbers for true and false positives, true and false negatives in this field validation are derived in the following way:

True positives. As this is a validation of the field procedure, we include all the cases who were screen positives (step 1) and confirmed by the neurologist as (febrile or afebrile) seizures (1030 = 958+38+34). These cases were not missed by the screening and must therefore be included in the total true positive number. Also, included are the 87 cases who were estimated to exist amongst the 4920 people who the rural doctor deemed as false positives. This estimated (adjusted) total is therefore 1117 (1030+87). This number will be used for calculating validity. The number of cases actually identified (crude number, 1030) will be used for calculating age and sex specific rates.

False positives. 6330 were screen positive cases, of whom 1117 were considered to be true positives and 234 were not taken into consideration (175 cases who were not seen by rural doctor +36 cases who were examined by the neurologist +23 cases with uncertain diagnosis). Therefore, the number of false positives is estimated to be 4979 (6330−1117−234). Accordingly, 6096 (4979+1117) screen positives will be used for the raw validity estimations.

False negatives and true negatives. The total number of negatives in the screening was 65 791. The number of false negatives within this group, i.e. patients with a history of epileptic seizures, but who were negative in the survey, was estimated, based on a review of a random sample of 904, to be 291 cases out of the total of 65 791 negatives. Therefore the number of true negatives was 65 500 (65 791−291).

To determine age and sex-specific validity rates, the crude values will be used. The age and sex specific predictive value will be calculated as the percentage of sex and age distribution of these 1030 cases, the denominator as the distribution of each group in the total of positives (6330). The rate of positive answers or suspects in the general population will be calculated using the distribution of these 6330 cases and the denominator the distribution of each group in the total population (72 121).

Results

A sensitivity of 79.3%, a specificity of 92.9%, a positive predictive value of 18.8%, a negative predictive value of 99.6% and a Youden's index of 0.79 were found (Table 2). Age and sex specific values are shown in Table 3 (based on the crude not adjusted values).

Predicted value, crude and adjusted. The calculation of this rate offers some other methodological difficulties. For instance, the overall positive predictive value of the clinic-based validation is 94.4%, but this may vary with varying relative proportions of numerator/denominator, which depend on the way the sample is selected, and this may introduce bias. In an attempt to adapt the sample utilized for the clinic-based validation as much as possible to reality, we adjusted the numbers to the corresponding proportions in the large community, as it was estimated in a previous local study (Placencia *et al.*, 1984). In the field

TABLE 2. FINDINGS FOR THE CLINIC-BASED AND FIELD VALIDATION

	Clinic-based (n = 150)		
	Crude (%)	*Adjusted (%)*	*Field (n = 72, 121) (%)*
Sensitivity	97.7	97.7	79.3
Specificity	92.1	92.1	92.9
Predictive value			
Positive	94.4	19.7	18.3
Negative	96.7	99.9	99.6
Total	95.3	92.2	92.7
Younden's index	0.9		0.79

TABLE 3 AGE AND SEX SPECIFIC RATES (PERCENTAGE) FOR POSITIVE ANSWER AND POSITIVE PREDICTIVE VALUE OF THE SCREENING AND THE CONFIRMED CASE RATE (PER 1000)

	Males			*Females*			*Total*		
Age in years	*PAR*	*CCR*	*PPV*	*PAR*	*CCR*	*PPV*	*PAR*	*CCR*	*PPV*
0–9	3.57	8.62	24.17	3.48	8.54	22.81	3.52	8.58	24.35
10–19	4.39	14.31	32.60	5.41	13.25	23.24	4.88	13.80	28.25
20–29	5.89	12.32	20.92	9.13	17.19	18.83	7.54	14.79	19.63
30–39	10.29	15.18	14.76	13.64	22.17	16.26	12.09	18.93	15.67
40–49	12.17	14.45	11.87	18.35	29.01	15.81	15.37	21.98	14.30
50–59	14.14	15.39	10.88	21.92	25.63	11.69	18.17	20.69	11.39
60–69	16.95	10.53	6.21	24.07	21.62	8.98	20.57	16.16	7.86
>70	20.39	10.85	5.32	25.79	17.43	6.76	23.06	14.10	6.11
Total	7.39	12.32	16.66	10.17	16.23	15.63	8.79	14.28	16.25

PAR = positive answer rate (per 100), CCR = confirmed cases rate (per 1000); PPV = positive predictive value (per 100)

validation, the total number of healthy subjects was estimated as 70 479 (4979 false positives + 65 500 true negatives) and the total number of cases estimated as 1408 (1117 true positives +291 false negatives). Thus, the ratio healthy/cases is 50.06 (70 479/1408). Using this value in the respective ratio of the clinic-based validation sample we obtained the adjusted ratio: 4355/87 (instead of the raw 63/87). By applying the raw proportion of five false positives and 58 true negatives to the 4355, the adjusted values of 346 and 4009 are obtained, respectively. With these estimated numbers, the adjusted values of the predictive value of the clinic-based validation were calculated and can be seen in Table 2, comparing them with the crude rates and with the rates obtained in the field survey.

DISCUSSION

Screening questionnaires have been used in a number of epidemiological studies of epilepsy published in the past decade. The earliest study using a two-tiered system of diagnosis was that of Rose *et al.* (1973), who included electroencephalogram (EEG) in the diagnostic definitions. Others since have used variations of this methodology. An influential World Health Organization (WHO) group (Osuntokun *et al.*, 1982; Schoenberg, 1982*a,b,c*) introduced a standardized neurological instrument for screening for a variety of neurological diseases, without recourse to EEG. This instrument had three questions relevant to epilepsy, which are for subjects of 7 yrs or older: (i) have you ever lost consciousness? (ii) have you ever had an episode where you lost contact with your surroundings? (iii) have you ever had shaking of your arms and legs which you could not control? In the last decade there have been a proliferation of neuro-epidemiological studies using this protocol (Osuntokun *et al.*, 1982; Cruz *et al.*, 1984; Placencia *et al.*, 1984; Pradilla *et al.*, 1984; Li *et al.*, 1985; Ponce *et al.*, 1985; Osuntokun *et al.*, 1987; Bharucha *et al.*, 1988; Chiofalo *et al.*, 1989).

Most investigations have screened using a house-to-house survey, postal or telephone survey, or have used a clinic population. Twenty of the published surveys provide some information about the validation of the screening procedures used. In 12, validation data are actually given (*see* Table 4 for references) and in the remaining eight validation is mentioned only briefly. In only two are sufficient details given to establish how the validation process was actually carried out (Zielinski, 1974; Placencia *et al.*, 1984). In Table 4 the findings from these 12 studies are shown. They report a sensitivity of the screening questionnaire between 77% and 100%, a specificity between 48% and 99%, and a predictive value between 16.3% and 90.8%.

Problems exist for all screening questionnaires in three particular areas. First, is the question of diagnostic confirmation. A particular issue in epilepsy is the use of the EEG. As epilepsy is essentially a clinical diagnosis and as many patients with epilepsy have normal EEGs, and many have an EEG which is inconclusive, the EEG is very limited as a screening tool (in contrast to its vital role in clinical practice). Its omission from screening procedures is therefore acceptable, and furthermore, its impracticality in a large-scale field study is clear. However, the clinical criteria on which the diagnosis is based must be clearly articulated, but only in a few studies has this issue been addressed. In the current survey, diagnostic criteria were specified on a proforma, made according to clinical features and were strictly adhered to (for details, *see* Placencia *et al.*, 1992*a,b*). We emphasize this as we consider it an important design aspect of the study. The definitions of epilepsy used are also important: particularly important are methods to differentiate febrile seizures, and also to account for active and inactive epilepsy, acute symptomatic and single seizures. Demographic details are needed to differentiate febrile seizures, and the clinical algorithms should specifically specify whether single seizures and acute symptomatic seizures are to be surveyed.

The second problem is that of sensitivity. In epilepsy, most screening questionnaires have concentrated on the detection of tonic clonic seizures. This is a relatively easy task, and there is usually high sensitivity. The detection of partial seizures is a more difficult problem, as their clinical manifestations are protean. Some screening instruments, used in the past, have not included questions likely to be sensitive to these cases. Often partial seizures coexist with tonic clonic attacks (i.e. secondarily generalized seizures), which may lessen but not abolish this under-reporting. The present questionnaire was piloted specifically among clinic patients with partial epilepsy, and a satisfactory sensitivity was recorded. The WHO questionnaire is an instrument for the detection of neurological morbidity which includes epilepsy as part of a wider screening process. Although sensi-

TABLE 4 PUBLISHED STUDIES OF INCIDENCE AND PREVALENCE OF EPILEPSY WHICH GAVE DATA ON THE VALIDATION OF SCREENING INSTRUMENTS

		Validation rates		
Author	*Location*	*Sensitivity*	*Specificity*	*Positive predictive value*
Bharucha *et al.* (1988)	Bombay, India	100.0	–	–
Carpio *et al* (1986)	Cumbe, Ecuador	93.0	–	–
Chiofalo *et al.* (1989)	Santiago, Chile	–	99.9	90.8
Cruz *et al.* (1984)	Quiroga, Ecuador	90.0	–	51.7
García-Pedroza *et al.* (1983)	Tlalpan, Mexico	79.0	10.0	19.5
Gutierrez *et al.* (1980)	Ajusco, Mexico	86.0	80.0	–
Osuntokun *et al.* (1982)	Aiyete, Nigeria	95.0	80.0	57.0
Osuntokun *et al.* (1987)	Igbo-Ora, Nigeria	95.0	80.0	–
Placencia *et al.* (1984)	Cangahua, Ecuador	96.3	48.0	27.1
Pradilla *et al.* (1984)	Giron, Colombia	90.0	68.0	86.8
Rowan and Hyman (1976)	Bronx, USA	77.0	–	–
Zielinski (1974)	Warsaw, Poland	85.5	84.0	–

tivities, specificities and predictive values have been calculated for all neurological disease, these have not been given for epilepsy alone.

The third problem is the contrasting one of specificity. The difficulty in designing seizure specific instruments is shown clearly, for instance, by the application of the WHO protocol. Apart from the atypical result reported by Chiofalo *et al.* (1989) of an astounding specificity of 99.9%, reported specificities have varied between 48% and 80% (Table 4). In these studies, therefore, between 20% and 52% of healthy individuals in the community will have been identified as possible cases, requiring specialist examination. The low specificity results in a large logistical effort to sieve out true cases and increasing potential for error.

It is because of the problems of obtaining satisfactory sensitivity and specificity that we feel that composite neuro-epidemiological screening questionnaires should be avoided; and that for epilepsy at least, a specific screening instrument for partial and generalized seizures is necessary. Although of great use in general neurological screening, we believe that composite screening instruments such as the WHO questionnaire have only a limited role in epilepsy.

We have designed a screening questionnaire specifically for epilepsy, initially of 20 questions, which, after clinic-based validation, was refined to nine questions. These were chosen to provide a good compromise between high specificity and sensitivity, both for partial and generalized seizures. These questions, however, were non-specific for both absence and myoclonic seizures; the inclusion of specific questions would have rendered the field survey impractical and produced a high rate of false positives. Patients with absence and myoclonic seizures are probably a very small proportion of cases, and many of these patients have coexistent seizure types (generalized convulsions) which would be detected by the questionnaire, it was felt that this would not jeopardize the exercise. Furthermore, the proportion of absence and myoclonic seizures detected (about 3%) is very similar to the proportion found in Western populations (Juul-Jensen and Foldspang, 1983; Sander *et al.*, 1990), suggesting to us that not many cases were missed.

The sensitivity, specificity and predictive values of this nine question instrument are presented here (sensitivity of 79.3%, specificity of 92.9%, positive predictive value of 18.3%, negative predictive value of 99.6% and a Youden's index of 0.79). The questionnaire was validated in this very large-scale trial, using quality control steps (steps 5 and 6) to detect false positive and false negative rates in the field. We were gratified to find specificity and sensitivity rates in the field validation to be similar to those of the clinic validation; and both satisfactory sensitivity and high specificity were achieved for the detection of epileptic attacks.

The results of this exercise encourage us in the belief that this epidemiological survey instrument is both effective and resilient, and will prove to be a useful addition to the neuro-epidemiologist's armamentarium.

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APPENDIX 1

Original screening questionnaire as used during the clinic-based validation

(1) Have you ever lost consciousness?
(2) Have you ever had attacks in which you loose contact with the surroundings?
(3) Have you ever had attacks of shaking of the arms or legs which you could not control?
(4) Have you ever had attacks in which you fall to the ground with loss of consciousness?
(5) Have you ever had attacks in which you fall and bite your tongue?
(6) Have you ever had attacks in which you fall and lose control of your bladder?
(7) Have you ever had attacks in which you fall and become pale?
(8) Have you ever had attacks in which you lose your memory for a short period of time?
(9) Have you ever had attacks of strange behaviour and loss of memory?
(10) Have you ever had brief attacks of shaking or trembling in one arm or leg or in the face?
(11) Have you ever had attacks of tingling or numbness which move up your arm, leg or body?
(12) Have you ever had attacks of jerkings which move up your arm, leg or body?
(13) Have you ever had attacks in which you lose contact with the surrounding and experience a feeling of unreality or dreaminess?
(14) Have you ever had attacks in which you lose contact with the surrounding and experience a sensation in which objects change shape or size?
(15) Have you ever had attacks in which you lose contact with the surrounding and experience abnormal visions?
(16) Have you ever had attacks in which you lose contact with the surrounding and experience abnormal sounds?
(17) Have you ever had attacks in which you lose contact with the surroundings and experience abnormal smells?
(18) Have you ever had attacks in which you behave momentarily in a confused fashion?
(19) Have you ever had attacks of palpitation?
(20) Have you ever been told that you have or had epilepsy or epiliptic fits?

APPENDIX 2

Screening questionnaire as used during the large-scale survey in the community

(1) Have you ever had attacks of shaking of the arms or legs which you could not control?
(2) Have you ever had attacks in which you fall and become pale?

Both question 1 and 2 must be affirmative to render the subject positive.

(3) Have you ever lost consciousness?
(4) Have you ever had attacks in which you fall with loss of consciousness?
(5) Have you ever had attacks in which you fall and bite your tongue?
(6) Have you ever had attacks in which you fall and lose control of your bladder?
(7) Have you ever had brief attacks of shaking or trembling in one arm or leg or in the face?
(8) Have you ever had attacks in which you lose contact with the surroundings and experience abnormal smells?
(9) Have you ever been told that you have or had epilepsy or epileptic fits?

Any question 3 to 9 if affirmative renders the subject positive.

Brain (1992), **115**, 795–807

BRAIN ENERGY METABOLISM IN BILATERAL PARAMEDIAN THALAMIC INFARCTS

A POSITRON EMISSION TOMOGRAPHY STUDY

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SUMMARY

Positron emission tomography (PET) studies of the cerebral metabolic rate of oxygen ($CMRO_2$) were performed in seven consecutive patients with bilateral paramedian thalamic infarcts (BPTI), selected on neuroradiological and clinical criteria. The latter consisted of sudden onset of coma or confusion followed by a persistent amnesia of varying severity, with or without language impairment and frontal lobe signs. There was a highly significant decrease of $CMRO_2$ for the whole cortex as well as for all the regions analysed: medial-frontal, latero-frontal, temporal, sensorimotor and posterior associative cortex. The mean regional metabolic ratios (region/whole cortex $CMRO_2$) were not significantly different from controls, indicating an essentially uniform effect in the cortex, except the sensorimotor ratio which was significantly increased. Diffuse cortical hypometabolism most likely reflects thalamo-cortical deafferentation secondary to damage to the 'non-specific' thalamic nuclei, while sparing of the latero-ventral thalamus presumably explains the relative preservation of the sensorimotor cortex metabolism. Although no clear-cut individual relationship was found between magnitude of cortical hypometabolism and the severity and pattern of neuropsychological impairment, the data suggest that the former underlies and/or reflects the latter. Further studies with higher resolution PET devices might shed more light on the relationships between distinct cognitive patterns and specific topography of cortical hypometabolism in BPTI patients.

INTRODUCTION

The entity termed bilateral paramedian thalamic infarcts (BPTI) was initially individualized from anatomical studies (Castaigne *et al.*, 1966, 1981; Lapresle and Haguenau, 1973), but a well-defined clinical syndrome with radiological criteria has subsequently emerged (Dehaene, 1982; Guberman and Stuss, 1983; Graff-Radford *et al.*, 1985*a*,*b*; Gentilini *et al.*, 1987; Meissner *et al.*, 1987; Bogousslavsky *et al.*, 1988). Bilateral paramedian thalamic infarcts are rare, but not exceptional, because occlusion of the thalamic paramedian arteries [which often arises from a common trunk at the initial segment of one posterior cerebral artery (PCA)], frequently occurs in the context of distal basilar or initial PCA occlusion (Graff-Radford *et al.*, 1984; Barkhof *et al.*, 1988; Mehler, 1989).

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Clinically, the BPTI syndrome is characterized by sudden onset of coma/stupor or confusion with an ensuing complex neuropsychological impairment made of apathy and amnesia of varying severity, sometimes referred to as 'thalamic dementia' (Castaigne *et al.*, 1966; De Boucaud *et al.*, 1968). Vertical gaze paresis is frequently but inconsistently observed.

The mechanism for the neuropsychological/behavioural impairment of BPTI, probably a consequence of damage to the medio-dorsal and/or intralaminar thalamic nuclei, has remained only speculative up to now (Delay *et al.*, 1961; Castaigne *et al.*, 1966; Schott *et al.*, 1980; Barbizet *et al.*, 1981; Winocur *et al.*, 1984; von Cramon *et al.*, 1985; Zola-Morgan and Squire, 1985; Stuss *et al.* 1988). Previously, focal or diffuse cortical hypometabolism ipsilateral to putaminal haemorrhage or thalamic stroke has been demonstrated by positron emission tomography (PET) in cognitively impaired patients (Baron *et al.*, 1986; Metter *et al.*, 1986). In progressive supranuclear palsy (PSP), a 'model' of degenerative subcortical dementia (Albert *et al.*, 1974), a diffuse cortical, preferentially frontal hypometabolism was revealed by PET (D'Antona *et al.*, 1985). In patients with frontal-like behaviour and lesions involving the globus pallidus bilaterally, a mild but significant frontal cortex hypometabolism has been reported (Laplane *et al.*, 1989). In all of these examples of subcortical lesions, the observed metabolic depression of the cerebral cortex was thought to underlie and/or reflect the behavioural impairment.

Is the behavioural impairment of BPTI similarly attended by a cortical hypometabolism? To address this issue, we have obtained clinical, neuropsychological, computerized tomography (CT) scan and/or magnetic resonance imaging (MRI) data in seven patients with BPTI in whom PET studies of cerebral blood flow (CBF) and oxygen consumption were performed.

PATIENTS AND METHODS

Patient selection criteria

Patients with the BPTI syndrome were selected on strict clinical and neuro-imaging criteria. The former were based on initial events: sudden onset of coma, stupor or confusion without prominent sensory-motor deficit, followed by gradual recovery with persistent apathy and amnesia. The presence of oculomotor disturbances was not an inclusion criteria.

The characteristic topography of lesions was assessed on CT and/or MRI scans: bilateral, but not necessarily symmetrical, thalamic infarction in the territory of the thalamoperforate arteries (Takahashi *et al.*, 1985, Meissner *et al.*, 1987). Patients with significant focal lesions elsewhere, except in other parts of the vertebrobasilar territory, were not included.

Patients

Seven patients, all males (mean age: 55 ± 11.3 yrs, range 44–75 yrs) were selected in a period that extended over 4 yrs because of the rarity of BPTI. Initial clinical presentations and examinations on the day of the PET study are summarized in Table 1. The interval of time from clinical onset to PET varied from 40 d to 8 yrs.

At the time of the PET study, two patients were untreated (Cases 1–3), while three patients (Cases 4–6) were on aspirin or anticoagulant treatment with or without cardiological treatment; one (Case 2) was on neuroleptics and lithium, and another (Case 7) on valpromide, all drugs which have no significant or documented effects on cerebral metabolism.

Formal neuropsychological tests were performed on all patients (except patient 4 because of major intellectual impairment), including tests of language, calculation, praxis, intellectual efficiency, memory and attention. The results of psychometric evaluation are presented in Table 2.

TABLE 1 CLINICAL DATA

			Initial clinical presentation			*Clinical presentation (PET day)*		
Patient	*Sex/age*	*Interval Stroke/PET*	*Coma*	*Sensory motor signs*	*Neuro-ophthalmology*	*Sensory motor signs*	*Neuro-ophthalmology*	*Etiology*
1	M/50	4 yrs	+	+ (R)	Parinaud	Ataxia (R)	Parinaud	Unknown
2	M/62	2 yrs	+	+ (L)	Parinaud	Ataxia (L), facial paresis (L)	Parinaud	FMD
3	M/75	7 mths	Confusion	–	–	–	–	Arterial hypertension
4	M/49	2 mths	+	+ (R)	III (L), myosis (R)	Ataxia (R), facial paresis (R), dysarthria	III (L)	Coronarography accident
5	M/61	40 d	+	+ (L)	Myosis (R-L)	–	Parinaud	Cardiac arrythmia
6	M/45	2 yrs	+	+ (R)	–	Ataxia (R), dysarthria	Lateral homonymous hemianopia (R)	Unknown
7	M/44	8 yrs	+	–	Myosis (R-L)	–	Parinaud	Unknown

R = right; L = left; FMD = fibromuscular dysplasia; + = present; – = absent.

TABLE 2. NEUROPSYCHOLOGICAL TESTS IN SIX PATIENTS

			Cases					
	Tests	*References*	*1*	*2*	*3*	*5*	*6*	*7*
Language	Word list generation	Spreen and Benton, 1969	–	–	–	+ + +	+	+ +
	Naming	Goodglass and Kaplan, 1972	–	–	–	–	+	–
	Similarities	Wechsler, 1955	+	+ +	–	+ + +	+ +	+ + +
Calculation		Wechsler, 1955	–	–	–	+ +	+ +	+ +
Praxis	Copy of Rey figure	Lezak, 1983	–	–	–	+ +	+ + +	+
Intellectual efficiency	PM47	Raven, 1956	–	–	–	+ + +	+ + +	+
Orientation in time and space		Wechsler and Stone, 1945	–	–	+ + +	+ + +	+	+
Memory	Wechsler Memory Scale	Wechsler and Stone, 1945	+ +	+	+ +	+	+ + +	+ + +
	Recall of Rey figure	Lezak, 1983	+ +	+ +	+ + +	+ +	+ + +	+ + +
Attentional matrix	Wisconsin Card Sorting Test	Grant and Berg, 1980	+	n.p.	+ + +	n.p.	+ +	+ + +
	Graphic alternating sequences	Luria, 1966	+	–	–	+ +	+ + +	+ +
	Bradyphrenia	Pillon *et al.*, 1988	+ +	–	–	+ +	+ + +	+ + +

The tests were not performed in patient 4 because of major intellectual impairment. – = no impairment; + = mild impairment; + + = moderate impairment; + + + = severe impairment; n.p. = not performed.

Computerized tomography scan and MRI

All the patients had one or more CT scans, including one on the day of stroke. In five patients, MRI was performed near the day of PET, using a superconducting MR imager operating at a field strength of 1.5T. Coronal, horizontal and sagittal 5 mm slices were taken every 7.5 mm, and T_1- and T_2-weighted sequences were used. In each of these five patients, the bilateral thalamic lesions established on the CT scan were also observed on the MRI. In all cases, the CT and MRI scans revealed bilateral thalamic infarcts centred on the thalamo-perforate artery territory (Takahashi *et al.*, 1985). However, the lesions differed in size and were often asymmetric in size of location or both, and were at times small (as in patient 3). As an illustration, Fig. 1 shows CT or MRI cuts depicting best the bilaterality of the thalamic lesion. The CT or MRI cuts were viewed against an anatomical atlas (Salamon and Huang, 1980) in order to localize more precisely the damaged thalamic nuclei. This anatomical localization remained approximate, however, because of (i) difficulties encountered in delineating precisely the borders of lesions; (ii) frequent third

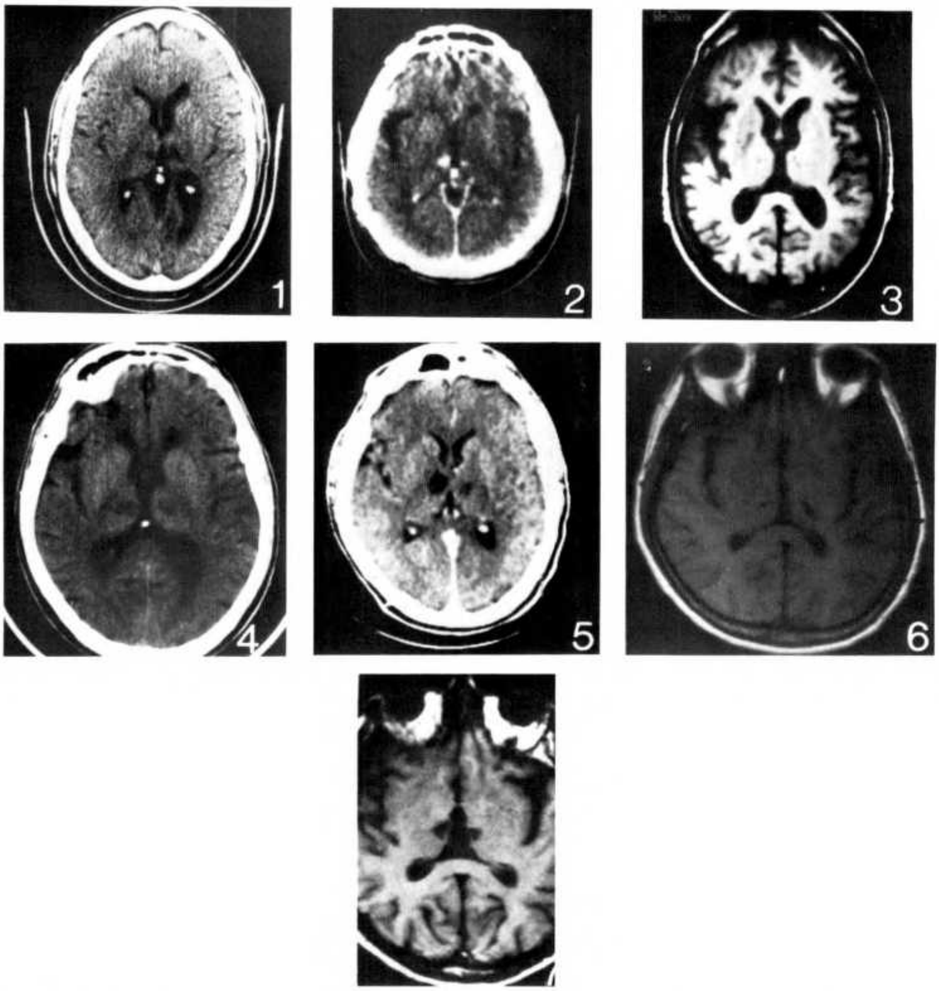

FIG. 1. Morphological neuroimaging data in the seven BPTI patients. The single CT scan or MRI cut depicting best the bilaterality of the paramedian thalamic lesion was selected in each patient. CT scan cuts were selected in patients 1, 2, 4, 5 (with contrast enhancement in patient 2) and MRI cuts (T_1-weighted) in patients 3, 6, 7. (In patient 3, the bilateral lesions were revealed by early CT scan at two different cuts.)

ventricle enlargement (presumably as a result of thalamic tissue loss); (iii) known variability in the size of the thalamic nuclei (Talairach *et al.*, 1967). Using this approach, we estimated that the medio-dorsal and intra-laminar nuclei were damaged in all the patients, while the ventral anterior, ventral lateral or centro-median nuclei were possibly involved in some. The CT scan of patients 1 and 6 revealed a hypodense lesion in the superficial territory of the left PCA, while patient 7 had a right cerebellar infarct. No other lesion was seen except some degree of diffuse cortical atrophy in four patients, which was rated as very mild in three of them (Cases 3, 6, 7) and mild in one (patient 4).

Positron emission tomography studies

In each of the seven patients, the regional cerebral metabolic rate of oxygen ($CMRO_2$) was measured using the $[^{15}O]CO_2$-$[^{15}O]O_2$ continuous inhalation method (Jones *et al.* 1976; Frackowiak *et al.*, 1980; Lebrun-Grandié *et al.*, 1983) and the multislice LETI-TTV01 time of the flight positron camera. Seven planes parallel to the orbitomeatal (OM) line and located respectively 10 mm, 25 mm, 40 mm, 55 mm, 70 mm, 85 mm and 100 mm above this line were obtained simultaneously. The axial and lateral resolutions were both equal to 13 mm full width half maximum (FWHM) with an undetected interslice of approximately 3 mm. The study was performed on subjects at rest with their eyes closed but ears unplugged, and reducing the external stimulation to a minimum. Correction for attenuation was carried out using ^{68}Ge-^{68}Ga transmission scans. During each of the two successive ^{15}O scans, blood samples were withdrawn in duplicate from a radial artery catheter, to measure the ^{15}O radioactive concentration in whole blood and plasma as well as the PaO_2, $PaCO_2$, pH, haematocrit and haemoglobin values.

The PET images were transformed pixel by pixel into quantitative CBF (ml/100 ml/min), oxygen extraction fraction (OEF) (dimensionless) and $CMRO_2$ (ml O_2/100 ml/min) images using the ^{15}O blood data and equations as described elsewhere (Jones *et al.*, 1976; Frackowiak *et al.*, 1980). In this study, correction of the OEF for unextracted intravascular labelled oxyhaemoglobin was not performed; however, the lack of difference in measured OEF between patients and controls (*see* Results) would have resulted in a roughly constant correction (Pantano *et al.*, 1985).

Positron emission tomography data analysis

Out of the seven transaxial PET scans, four typical cortical planes were selected from each PET study, using the atlas of the human brain of Matsui and Hirano (1978). This atlas was used because it is based on the OM line. These planes corresponded to the 'fronto-basal plane', the 'basal ganglia' plane, the 'low centrum semi-ovale' plane and the 'high centrum semi-ovale' plane. Circular regions of interest (ROI), 3 cm^2 in size were positioned over these four selected planes, using a standardized method detailed elsewhere (Samson *et al.*, 1986; Laplane *et al.* 1989). The mean cortical $CMRO_2$ value was calculated as the average of all the cortical ROIs over the four planes. Several functional regions (after grouping of ROIs) were defined according to anatomical regions. The ROIs positioned in infarcted areas were excluded from the calculation of cortical global or regional $CMRO_2$. Five large anatomical regions (mean of right and left areas except for the medio-frontal region) were defined: medio-frontal, latero-frontal, temporal, sensorimotor, posterior associative cortex (Salamon *et al.*, 1987; Laplane *et al.*, 1989). The most posterior ROIs (located in the medial occipital areas) were excluded from analysis because large vascular pools in these regions often result in spurious $CMRO_2$ values.

The data analysis was carried out not only on the absolute $CMRO_2$ values, but also on 'metabolic indices' or 'ratios', calculated as $rCMRO_2$ divided by the average cortical $CMRO_2$, which represents the regional pattern of brain metabolism superimposed on global changes.

To investigate the CBF/$CMRO_2$ coupling in the cerebral cortex, we also analysed the CBF and the OEF in a single cortical plane (the 'basal ganglia' cut).

The cerebellum data were analysed on the plane OM ± 10 mm, using 9.2 cm^2 ROIs positioned on both cerebellar hemispheres as described elsewhere (Pantano *et al.*, 1986) except in patient 7 in whom only the left cerebellar hemisphere was studied because of a right cerebellar infarct. In patient 4, cerebellar PET data were unavailable due to a technical problem affecting one detector ring during scanning.

Statistical analysis

In order to account for well-described age-effects on cerebral oxygen metabolism (Leenders *et al.*, 1990), the patient data were compared with control values obtained in seven healthy, normally functioning volunteers (six males, one female) free of cerebrovascular risk factors, matched for age to the seven patients and studied over the same period in time. Informed consent was obtained in all cases. Following individual matching of each patient to one control subject according to age rank, we used paired *t* tests to test the mean differences in both absolute values and regional indices between pairs of subjects against zero; paired tests are more efficient than unpaired comparison of means to account for the confounding factor (Snedecor and Cochran, 1980).

RESULTS

Mean absolute cortical $CMRO_2$ values

There was a marked, statistically significant decrease of the global cortical $CMRO_2$ in the BPTI group (mean decrease of 24.7%) compared with controls (*see* Fig. 2). The

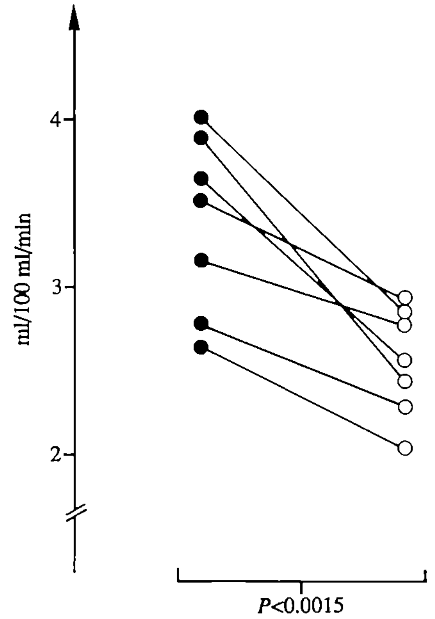

FIG. 2. Individual whole cortex $CMRO_2$ values (average of the four cortical planes) are shown in the seven BPTI patients (open circles; n = 7) and in the seven age-matched controls (closed circles; n = 7). For clarity, lines join the matched patient-control pairs. Using paired *t* test, a highly significant metabolic decrease in the patient group ($P < 0.0015$) compared with controls was shown Statistical significance was also obtained when using unpaired *t* test on means ($P < 0.004$).

analysis of the regional cortical $CMRO_2$ values disclosed a highly significant metabolic depression in all the regions analysed without clear-cut regional pre-eminence of the hypometabolism (Fig. 3). The statistical significance of these findings is unaltered even if corrected for multiple comparisons. Additionally, use of unpaired instead of paired *t* tests led to the same conclusions.

Mean regional metabolic indices

There was no significant difference between the control and the patient groups, save for a significant increase of the metabolic ratio for the sensorimotor cortex (Fig. 4).

CBF-CMRO$_2$ coupling on the plane OM+40 mm (the 'basal ganglia' cut)

There was a reduction of cortical CBF in the patient group compared with the controls (31.9 ± 6 and 37.6 ± 5.3 ml/100 ml/min, mean ± SD, respectively) which was of the same magnitude (−15%) as that of the metabolic depression (−20.1% on the same plane), indicating an essentially unchanged CBF-$CMRO_2$ 'coupling' (Lebrun-Grandié *et al.*, 1983; Sette *et al.*, 1989); this was also shown by the lack of significant difference between the mean OEF in the two groups (0.51 ± 0.09 and 0.49 ± 0.05, means ± SD, in the patient and control group, respectively).

Cerebellum data

As in the cerebral cortex, there was a reduction in both CBF and $CMRO_2$ in the cerebellum (−12.6% and −15.2%, respectively) less prominent than in the cerebral cortex and statistically significant for the $CMRO_2$ values only ($P < 0.05$) (CBF and $CMRO_2$ in the patients: 41.8 ± 9.1 ml/100 ml/min and 3.4 ± 0.4 ml O_2/100 ml/min; CBF and $CMRO_2$ in the controls: 47.9 ± 12.9 ml/100 ml/min, 4.0 ± 0.8 ml O_2/100 ml/min, mean ± SD respectively). The OEF was unchanged.

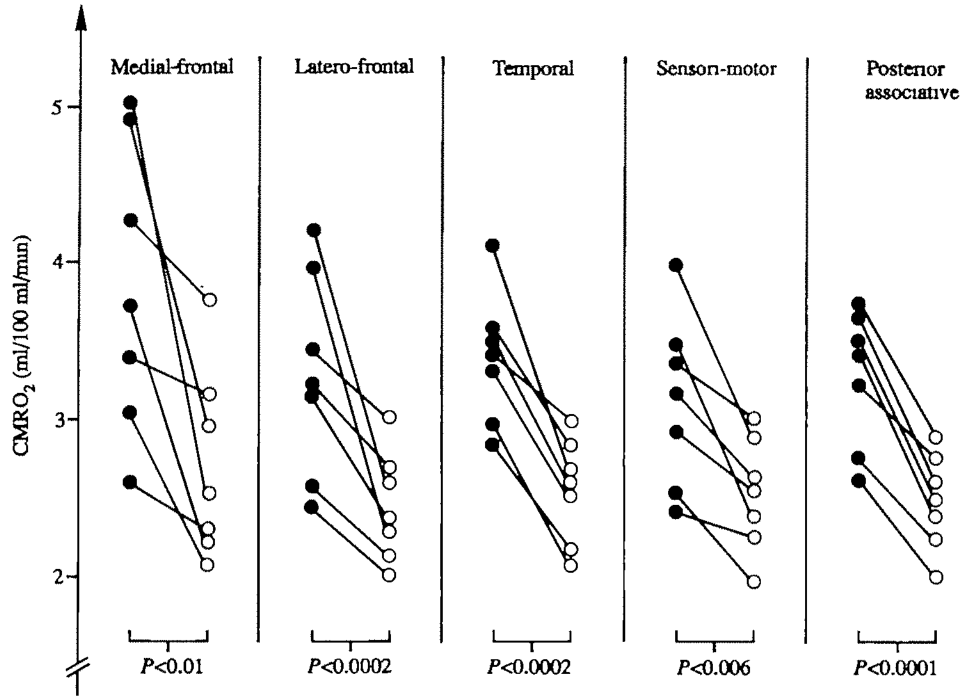

FIG. 3. Individual cortical $CMRO_2$ values in medial-frontal, latero-frontal, temporal, sensorimotor and posterior-associative cortex in the seven pairs of matched BPTI patients (open circles) and controls (closed circles), joined by lines, are shown. Compared with controls, there was a significant hypometabolism in all the cortical regions studied (the *P* values indicate paired *t* tests, uncorrected for multiple comparisons; differences remain statistically significant if unpaired *t* tests are used)

DISCUSSION

In our sample of seven patients with BPTI, PET disclosed a diffuse cortical hypometabolism which was highly significant compared with seven age-matched controls. Across the whole sample, there was no noticeable regional pre-eminence of this cortical hypometabolism, as shown by the analysis of both the absolute metabolic rates and the metabolic ratios (Figs 3, 4), although the latter revealed a significant increase of sensorimotor cortex metabolic index. Although we could not match patients and controls for the degree of cortical atrophy, the latter would not entirely account for our findings, based on the following facts: (i) cortical atrophy was absent or very mild in three patients and mild in one only (*see* Fig. 1); (ii) unilateral thalamic lesions, including stereotaxic thalamotomy, are known to induce ipsilateral cortical hypometabolism regardless of cortical atrophy (Baron *et al.*, 1986, 1989); (iii) cortical metabolism has been reported as unchanged in seven patients with bilateral lenticular necrosis, three of whom had moderate-to-severe atrophy (Laplane *et al.*, 1989); (iv) cortical atrophy would hardly explain the reduction in cerebellar hypometabolism present in our sample. The latter presumably reflects secondary transneuronal effects of the neocortical hypometabolism via the cortico-ponto-cerebellar pathway, rather than retrograde thalamo-cerebellar effects (Biersack *et al.*, 1987; Pappata *et al.*, 1990); direct cerebellar damage was present in

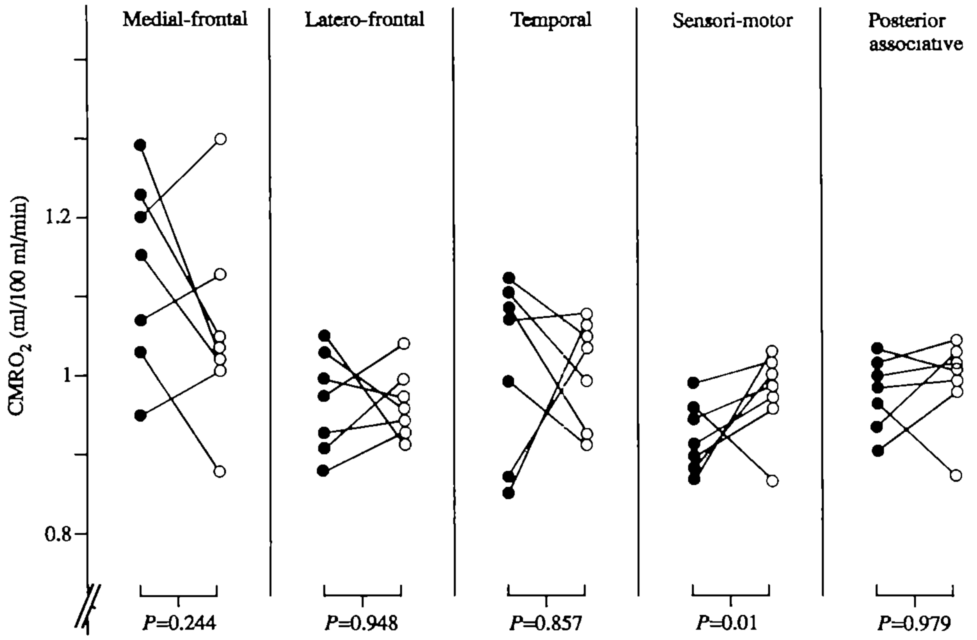

FIG. 4. Individual regional metabolic ratios (regional CMRO$_2$ whole cortex) in each of the cortical regions depicted in Fig. 3 are shown There was no significant difference between the patients (open circles) and controls (closed circles) ratios ($P > 0.05$), except in the sensorimotor area where a significant increase was seen ($P = 0.01$) in the patient group.

only one patient, while brainstem damage was too limited to cause more proximal cerebellar de-afferentation. The depression in cortical CMRO$_2$ was matched to a similar reduction in CBF, consistent with preserved perfusion-metabolism coupling in de-afferented brain areas (Baron *et al.*, 1984). Previously, only single case reports have mentioned a diffuse cortical hypometabolism in BPTI, as measured by PET in one patient and as inferred from reduced CBF in another case studied by single photon emission tomography (Bewermeyer *et al.*, 1985; Muller *et al.*, 1989); Rousseaux *et al.* (1989), using the latter technique, also briefly alluded to a cortical hypoperfusion in three out of four BPTI cases.

Although close inspection of the available CT/MRI scans in our sample did not disclose clear-cut subthalamic lesions, the clinical data indicate that the lesion slightly extended to the subthalamic part of the thalamoperforate arterial territory (Takahashi *et al.*, 1985). Thus, it is possible that the cortical metabolic depression seen here is due in part to such non-thalamic lesions. However, lesions of the locus coeruleus or raphe nuclei in the rat do not result in major effects on cortical glucose use or oxygen consumption (Dahlgren *et al.*, 1981; Savaki *et al.*, 1984). Conversely, cortical hypometabolism has been repeatedly documented following unilateral thalamic stroke in humans (Baron *et al.*, 1986) and stereotaxic lesions in rats (Girault *et al.*, 1985) and humans (Baron *et al.*, 1989), while electric stimulation of the parafascicular nucleus in rats increases cortical metabolism (Aiko *et al.*, 1987); thalamic stimulation has similar effects in humans (Portenoy *et al.*, 1986; Katayama *et al.*, 1986).

The diffuse cortical hypometabolism seen after unilateral thalamic lesions has been ascribed to cortical de-afferentation (Baron *et al.*, 1986, 1989; Rousseaux *et al.*, 1986; Perani *et al.*, 1988) with the ipsilateral effect related to thalamo-cortical system damage, and the less conspicuous contralateral effect to transcallosal spread of functional depression (Feeney and Baron, 1986). Following unilateral lesion of the nucleus basalis of Meynert in baboons, strikingly similar cortical metabolic effects have been reported and ascribed to cholinergic de-afferentation (Kiyosawa *et al.*, 1989). In subcortical lesions, the observed cortical hypometabolism presumably underlies or reflects cognitive/behavioural impairment, e.g. aphasia in left putaminal (Metter *et al.*, 1986) or thalamic stroke, neglect in right thalamic stroke (Baron *et al.*, 1986) and frontal lobe syndrome in bipallidal lesions (Laplane *et al.*, 1989) and PSP (D'Antona *et al.*, 1985).

In the BPTI syndrome, cortical hypometabolism is both substantial (approximately −25%) and diffuse over the whole cortical ribbon, without consistent regional accentuation in the entire group, in agreement with findings in unilateral thalamic lesions (Baron *et al.*, 1986). Abundant thalamo-cortical fibres originate from the so-called 'non-specific' nuclei which include the intralaminar, medio-dorsal, parafascicular and centro-medial nuclei (Herkenham, 1986; Macchi *et al.*, 1986), all typically damaged in paramedian artery territory infarction, based on pathological studies (Percheron, 1976; Castaigne *et al.*, 1981). Although we cannot establish in detail the thalamic nuclei damaged in each one of our patients, the medio-dorsal and intralaminar nuclei were apparently involved in all (*see* Fig. 1). These nuclei generally project to large parts of the neocortex, but with lesser density to the primary somatosensory cortex (Jones, 1983), which is connected mainly to the ventro-postero-lateral (VPL) nucleus (a 'specific' thalamic nucleus). The relative preservation of the oxygen metabolism in the sensorimotor area (Fig. 4) is likely due to the distribution of damage in BPTI, which typically spares the VPL. Conversely, thalamic lesions damaging the VPL result in no measurable depression of cortical energy metabolism (Chabriat *et al.*, 1990). Another interpretation of the diffuse neocortical effects with relative sparing of the somatosensory area would implicate thalamic nuclei with more circumscribed, but strategic cortical projections, whose damage would disrupt interconnected cortico-cortical distributed networks, e.g. the parieto-prefrontal network after medio-dorsal nucleus lesion.

Regardless of its precise mechanism, the cortical metabolic depression observed here is presumably related to the neuropsychological impairment. In all our patients, memory was significantly impaired and some degree of mental inertia was present. However, it was not possible to investigate the quantitative relationship between the degree of neuropsychological impairment and that of cortical hypometabolism, because formal quantitation of the former was often impossible due to severity of the deficit. With respect to specific tasks, four patients had language impairment, which was explained in two by a severe attention and memory deficit; in the remaining two patients, the $CMRO_2$ in the left temporal lobe was not clearly different from that measured in the three patients without language disturbance. Marked frontal lobe signs were present in five patients, but preferential frontal lobe hypometabolism was present neither in the whole group nor in this 'frontal' subgroup (although a slight, non-significant decrease of the medial-frontal metabolic index may be noticed, *see* Fig. 4); however, this does not exclude the possibility that individual BPTI patients may occasionally exhibit a more prominent frontal hypometabolism. Our findings in BPTI are reminiscent of PSP, where frontal predominance of cortical hypometabolism is mild despite frequent prominent frontal lobe syndrome (Blin *et al.*, 1990), suggesting that apparently 'focal' neuropsychological impairment in subcortical lesions is attended by a diffuse cortical hypometabolism with only slight corresponding focal accentuation. It must be made clear, however, that, due to the limited spatial resolution of our PET device, more focal hypometabolism may have been missed in individual patients. Further studies of BPTI patients with better resolution devices may establish more refined relationships between distinct patterns of cognitive impairment and hypometabolism in specifically assessed cortical areas.

In our limited patient sample, we found no clear-cut relationship between the severity of the global cortical hypometabolism and time elapsed since clinical onset (as assessed by linear regression, $r = 0.155$), indicating no obvious trend for recovery. This conflicts with earlier findings in neuropsychologically impaired patients with unilateral thalamic lesions (Baron *et al.*, 1989) and could imply that simultaneously bilateral lesions may prevent or interfere with metabolic recovery, in accordance with the fact that BPTI patients remain neuropsychologically impaired for extended periods. However, after the initial state of coma or confusion, a clinical recovery, albeit partial, was the rule in our cases (*see also* Meissner *et al.* 1987), but none was studied with PET within the first month, a critical period for metabolic recovery.

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A 2-DEOXYGLUCOSE STUDY OF THE EFFECTS OF DOPAMINE AGONISTS ON THE PARKINSONIAN PRIMATE BRAIN

IMPLICATIONS FOR THE NEURAL MECHANISMS THAT MEDIATE DOPAMINE AGONIST-INDUCED DYSKINESIA

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SUMMARY

The neural mechanisms that underlie both the anti-parkinsonian effects of dopamine agonists and dopamine agonist-induced dyskinesia were studied in parkinsonian primates, using the regional brain uptake of [^{3}H]2-deoxyglucose (2-DG).

Parkinsonian symptoms were induced in monkeys by the administration of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Some of the animals received chronic dopamine replacement therapy for at least 3 mths, which resulted in the appearance of peak-dose dyskinesia. The remaining animals spent an equivalent period of time relatively unexposed to dopaminergic agents, receiving only therapeutic doses, and at no time showed any signs of dopamine agonist-induced dyskinesia. The 2-DG metabolic mapping technique was applied to all of these animals shortly following the administration of a dose of dopamine agonist which was sufficient to alleviate their parkinsonian symptoms and to induce dyskinesia in those prone to this complication. The 2-DG uptake technique permits the autoradiographic measurement of local cerebral glucose uptake which was used as an index of regional synaptic activity. The resultant autoradiographs were compared with those from a previous study which examined 2-DG uptake in parkinsonian and normal brains from animals which had not received dopamine agonists prior to the terminal 2-DG uptake procedure.

The pattern of 2-DG uptake in the animals which received a dopamine agonist prior to the terminal procedure was strikingly different to both of the other groups. The most affected structure was the subthalamic nucleus which showed a dramatic increase in 2-DG uptake in animals exposed to dopamine agonist immediately prior to the terminal procedure, especially in the ventral tip of the nucleus. The medial pallidal segment also showed relatively greater levels of 2-DG uptake in the dopamine agonist group compared with the untreated parkinsonian state whereas, in contrast, the lateral pallidal segment showed decreased levels of 2-DG uptake.

The parkinsonian animals which had been sacrificed after receiving a dopamine agonist were split into three groups on the basis of their response to the agonist. The first group had their parkinsonism reversed and appeared clinically normal. The remaining animals had their parkinsonism reversed by the dopamine agonist but showed dyskinesia at peak dose. These animals were allotted to two further groups depending on whether their dyskinesia was of a choreic or dystonic nature. The increased levels of 2-DG uptake seen in the subthalamic nucleus were greater in animals where the administration of the dopamine agonist resulted in peak-dose dyskinesia, in particular when the dyskinesia was of a dystonic nature.

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The results suggest that underactivity of the subthalamic nucleus underlies dopamine agonist-induced dyskinesia. This probably results in lowered activity in the medial pallidal segment which projects to the motor nuclei of the thalamus.

INTRODUCTION

Dopamine replacement therapy with either levodopa or direct dopamine agonists is the most effective and widely used treatment for Parkinson's disease. This form of treatment is, however, not without limitations. In the long-term management of many parkinsonian cases a number of phenomena frequently occur which limit the effectiveness of the drug treatment. These phenomena include 'wearing-off' and 'on-off' effects and the occurrence of dyskinesias (Marsden and Parkes, 1976, 1977). Dyskinesias are most commonly seen at peak dose and the physical manifestation may vary considerably, being of a ballistic, or dystonic nature.

The mechanisms which mediate dopamine agonist-induced dyskinesias are far from understood. It has been speculated that the condition may arise from altered sensitivity of dopamine receptors on the grounds that the patient's dopamine systems appear to be overstimulated, and that dopamine receptors are known to increase in number following chronic blockade or denervation (Carlsson, 1970). There is, however, little direct experimental evidence to support this hypothesis.

Hypotheses concerning the pathophysiological mechanisms which underlie dopamine agonist-induced dyskinesia can now be tested directly following the recent development of an excellent primate model of the condition. Systemic administration of the neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), to macaque monkeys results in selective destruction of the dopamine-containing cells of the midbrain and occasionally the noradrenergic cells in the locus coeruleus (Burns *et al.*, 1983; Mitchell *et al.*, 1985*a*). In addition to having pathology which closely resembles that seen in humans with idiopathic Parkinson's disease, macaque monkeys treated in this way also show similar symptoms and responses to drug therapy. Thus, administration of dopamine agonists to MPTP-treated primates reverses their parkinsonian symptoms, and prolonged treatment results in the appearance of peak-dose dyskinesia (Bédard *et al.*, 1986, Clarke *et al.*, 1987, 1989).

In this paper we describe experiments undertaken to investigate the brain mechanisms which mediate peak-dose dyskinesia in the MPTP-treated monkey using the 2-deoxyglucose 2-DG metabolic mapping technique (Sokoloff *et al.*, 1977). This technique entails the administration of a radiolabelled analogue of glucose, 2-DG, during the active expression of a movement disorder. The regional uptake of 2-DG can then be visualized autoradiographically and quantified densitometrically. The degree of labelling acts as an index of metabolic activity and, by implication, of neuronal electrical activity.

We have previously applied this technique to study the pathophysiological mechanisms which mediate experimental chorea and ballism induced by the regional manipulation of neurotransmission in the primate (Mitchell *et al.*, 1985*b*,*c*, 1990). The results of this work suggested that these dyskinesias are mediated via abnormal activity in the subthalamic nucleus, medial segment of the globus pallidus and the ventral anterior-ventrolateral (VA-VL) thalamic complex. Both the subthalamic nucleus and the medial pallidal segment appear to be underactive in these conditions. Similarly, we have studied the neural mechanisms that mediate parkinsonism in the MPTP-treated monkey (Mitchell *et al.*, 1989*b*). This work suggested that parkinsonism is mediated by the same anatomical circuit as that which underlies dyskinesia, but in this instance the subthalamic nucleus and the medial pallidal segment are abnormally overactive.

In the present study, the 2-DG technique was applied to parkinsonian primates during the active expression of dopamine agonist-induced dyskinesia. The experimental design is complicated by the presence of three major variables: parkinsonism, dopamine agonist and dyskinesia. In order to aid interpretation of the results, autoradiographs from a previous experiment (Mitchell *et al.*, 1989*b*) were also analysed and these data are also presented. These data show the uptake of 2-DG in primates rendered hemi-parkinsonian by the unilateral injection of MPTP into the carotid artery. This procedure leads to unilateral destruction of the ascending dopaminergic system ipsilateral to the injection but leaves the contralateral side of the brain relatively intact. These animals did not receive a dopamine agonist prior to the terminal procedure and thus serve to give an indication of 2-DG uptake in both untreated parkinsonian and normal brains.

A separate group of parkinsonian animals received a dopamine agonist just prior to the terminal procedure which reversed their parkinsonian symptoms without resulting in the appearance of dyskinesia. These animals enabled the effect of a dopamine agonist on 2-DG uptake in the parkinsonian brain to be differentiated from the effects of the expression of dyskinesia on 2-DG uptake. In addition, the animals which had peak-dose dyskinesia have been subdivided into those which exhibited chorea and those which had dystonia.

METHODS

Preparation of model

Nine cynomolgus monkeys (*Macaca fascicularis*) of both sexes, weighing 5–8 kg were used in this experiment. Eight of the animals were injected with MPTP hydrochloride (Research Biochemicals, Natick, MA, USA) via the saphenous vein under general anaesthesia (ketamine, i.m.). Weekly injections of 2 mg/kg were given until the animals reached a marked but stable parkinsonian state. The cumulative dose for the animals ranged from 4 mg to 22 mg. The remaining animal (CYN 143) received a unilateral intra-carotid infusion of MPTP under genral anaesthesia according to the method of Clarke *et al.* (1989).

The animals were allotted to one of two groups once a stable parkinsonian condition had been achieved. The first group ($n = 6$) received regular dosing with dopamine agonists, either levodopa plus a peripheral decarboxylase inhibitor (Sinemet, Merck, Sharp and Dhome, UK) or apomorphine, three times a day for at least 3 mths. Such treatment resulted in the development of dyskinesia at peak dose. Dopamine agonists were only administered to the second group of animals on an *ad hoc* basis for therapeutic purposes and on a few occasions in the week prior to the terminal experiment. This enabled a dose of agonist to be determined which reversed the parkinsonism but which did not result in the appearance of any abnormal motor behaviour.

Procedure with 2-DG

Following an overnight fast, each animal received a dose of either levodopa (90–200 mg/kg p.o.) or apomorphine (0.2–0.93 mg/kg s.c.), the full details of which are given in Table 1. At peak-effect, a single i.v. pulse of 2–3 mCi/kg [^{3}H]2-DG (2-deoxy-2,6-[^{3}H]glucose, specific activity 30 Ci/mmol, Amersham, UK) in sterile saline was given. The animals were then left undisturbed for 45 min during which their behaviour was monitored. During this period six of the animals exhibited peak-dose dyskinesia whilst the other three animals appeared clinically normal. After 45 min an i.v. overdose of sodium pentobarbitone (Sagatal, May and Baker, UK) was administered. The brains were frozen *in situ* in isopentane at −40°C. The tissue was blocked stereotactically and the brains exposed by careful drilling. Coronal sections of

TABLE 1 THE DOSE OF DOPAMINE AGONIST ADMINISTERED TO EACH ANIMAL JUST PRIOR TO THE TERMINAL PROCEDURE AND THE RESULTANT CLINICAL STATE

*Animals**	*Drug/dose*	*Clinical state*
CYN 159	90.0 mg levodopa	Clinically normal
CYN 154	0.35 mg apomorphine	Clinically normal
CYN 170	0.20 mg apomorphine	Clinically normal
CYN 112	125.0 mg levodopa	Choreic
CYN 133	0.80 mg apomorphine	Choreic
CYN 116	0.93 mg apomorphine	Choreic
CYN 114	200.0 mg levodopa	Dystonic
CYN 143	0.80 mg apomorphine	Hemi-dystonic
CYN 156	0.90 mg apomorphine	Dystonic
CYN 131	No dopamine agonist	Hemi-parkinsonian*
CYN 136	No dopamine agonist	Hemi-parkinsonian*
CYN 144	No dopamine agonist	Hemi-parkinsonian*

*Animals previously described in Mitchell *et al.* (1989*b*)

whole brain were cut at 20 μm thickness on a cryostat maintained at −20°C. These were thaw-mounted onto gelatine-subbed slides, collectively freeze-dried and then sealed in X-ray cassettes loaded with Hyperfilm (Amersham, UK). The films were exposed for approximately 45 d and then developed with Kodak D19 and fixed with a universal fixative. The parent sections were stained with cresyl violet for histological examination.

Image analysis and densitometry

The resultant autoradiographs were examined, using an image analysis system (Seescan, UK), and optical density measurements taken. For each region examined optical density (OD) measurements were taken bilaterally from at least 10 autoradiographs. Each of these readings was then divided by the OD of the corpus callosum in order to calculate an OD ratio. Optical density ratios have been shown to bear a linear relationship to local cerebral glucose utilization across a wide range of isotope dose and exposure times and can, therefore, facilitate cross-animal comparisons (Sharp *et al.*, 1983; Mitchell and Crossman, 1984). For each animal, all of the OD ratios for each structure examined were averaged to give mean OD ratios, except where the animal had received a unilateral injection of MPTP. In this case, each side of the brain was treated as a separate subject and mean OD ratios for the structure on either side of the brain calculated.

To test for differences in OD ratio between the animals which received dopamine agonists and the untreated parkinsonian animals *t* tests were used (those unilateral parkinsonian animals which were previously reported in Mitchell *et al.*, 1989*b*). A one-way analysis of variance followed by the Tukey honestly significant differences multiple comparison test were used for differences in OD ratios between the three groups of parkinsonian animals which received a dopamine agonist, namely the non-dyskinetic, choreic and dystonic groups.

RESULTS

Clinical state of animals

Intravenous administration of MPTP led to the development of parkinsonian symptoms as previously described (Mitchell *et al.*, 1989*b*). At the end of the administration regime the animals exhibited marked hypokinesia, bradykinesia, rigidity and a stooped posture. There was a lack of mobility of facial expression, diminished blinking and decreased vocalization. The condition of the animals was judged to be equivalent to stage III–IV on the Hoehn and Yahr parkinsonian rating scale for man (Hoehn and Yahr, 1967). Unilateral infusion of MPTP into the carotid artery (CYN 143), produced contralateral parkinsonism. The affected limbs appeared hypokinetic, rigid and exhibited postural tremor. The upper limb was typically held adducted at the shoulder and flexed at the wrist and elbow. The normal limb was favoured during reaching and grasping. During spontaneous locomotion there was a tendency to circle towards the lesioned side.

Administration of low doses of dopamine agonist to all of these animals initially ameliorated the parkinsonian symptoms. Chronic dopamine agonist therapy in six of the animals, however, resulted in the appearance of peak-dose dyskinesia as previously reported (Clarke *et al.*, 1987, 1989; Boyce *et al.*, 1990). The dose of dopamine agonist administered to each animal immediately prior to the terminal procedure was based upon the minimal dose needed to reverse the animal's parkinsonism. Since this dose varied across the animals it was not possible to administer a standardized amount of dopamine agonist. It should be noted that dopamine agonists only result in dyskinesia following prolonged treatment (Clarke *et al.*, 1987, 1989; Boyce *et al.*, 1990). It is therefore unlikely that the absence of dyskinesia in the animals which did not receive prolonged dopamine agonist treatment was due to the dose of agonist used.

The behaviour of the animals during the 45 min period of 2-DG uptake that immediately preceded the terminal procedure is summarized in Table 1. In three of the animals (CYN 159, CYN 154, CYN 170), the dopamine agonist merely alleviated their parkinsonian symptoms. These animals exhibited no parkinsonian or dyskinetic symptoms, moved freely around the observation cage, and appeared to be clinically normal. In the remaining six animals alleviation of parkinsonism was accompanied by dyskinetic movements for most of the duration of the 45 min period of 2-DG uptake. Three of these animals (CYN 112, CYN 133, CYN 116), showed dyskinetic movements which were primarily choreic in nature. The choreic movements typically affected all limbs, the movements being in the form of alternate plantar-flexion and dorsi-flexion and eversion/inversion of the foot accompanied by flexion/extension of the knee and abduction/adduction of the hip. The three other dyskinetic animals showed dyskinetic movements which were primarily dystonic in nature. In two of the animals (CYN 114, CYN 156), the dystonia took the form of sustained flexion of the hips and knees and adduction of the hips. The remaining animal (CYN 143), which had received a unilateral intra-carotid injection of MPTP, became hemi-dystonic. This animal exhibited torticollis, its head being consistently turned away from the lesioned side. The limbs contralateral to the lesion were also dystonic, the lower limb being adducted and flexed at the hip and flexed at the knee. The left upper limb was adducted and extended at the shoulder, and flexed at the elbow.

Histology

Administration of MPTP resulted in a pattern of neuronal damage as previously reported (Burns *et al.*, 1983; Mitchell *et al.*, 1985*a*). Examination of the cresyl violet stained sections revealed an almost total loss of pigmented neurons from the midbrain tegmentum in the animals which received MPTP via the saphenous vein. The lesion in the animal which received a unilateral intra-carotid injection was restricted to the dopaminergic neurons on the side of the brain ipsilateral to the injection.

Densitometric analysis

Uptake of 2-DG in parkinsonian brain following administration of dopamine agonist. The effect of a dopamine agonist on 2-DG uptake in the parkinsonian brain is shown in Table 2. This table compares the level of regional 2-DG uptake (expressed in terms of OD ratios) in parkinsonian animals which received a dopamine agonist in the 45 min period prior to the terminal procedure (i.e. all nine animals in the current study) and parkinsonian animals which received no agonist (previously reported in Mitchell *et al.*, 1989*b*). The animals in the no-agonist group had received a unilateral intra-carotid injection of MPTP in order to produce a hemi-parkinsonian model. Optical density ratios are presented for both the parkinsonian and non-parkinsonian sides of the brain.

TABLE 2 THE EFFECT OF DOPAMINE AGONIST TREATMENT ON 2-DG UPTAKE IN PARKINSONIAN ANIMALS

Data are presented from 12 parkinsonian animals. Nine of these animals received a dopamine agonist just prior to the terminal 2-DG procedure (i.e. the animals were sacrificed on treatment). The data are compared with 2-DG uptake data from three parkinsonian animals which did not receive a dopamine agonist (i.e. sacrificed off treatment when parkinsonian symptoms were present). These three animals were rendered unilaterally parkinsonian by a unilateral intra-carotid injection of MPTP. Data for the parkinsonian and non-parkinsonian sides of the brain are presented.

The results are expressed in terms of OD ratios. Numbers are means and standard errors.

	Unilateral parkinsonian (n = 3) (no dopamine agonist)		
	Non-parkinsonian side	*Parkinsonian side*	*Parkinsonian + dopamine agonist (n = 9)*
CD	3.93±0.05	4.20±0.14	3.73±0.22
PUT	3.90±0.09	4.27±0.17	3.81±0.22
GPL	2.13±0.16	2.71±0.10	2.30±0.07**
STN	3.18±0.31	2.87±0.26	4.15±0.22*
STN-V	3.39±0.29	3.04±0.26	4.68±0.25*
GPM	2.02±0.12	2.12±0.01	2.45±0.08*
VA-VL	2.53±0.20	2.76±0.19	2.54±0.09
SN	2.29±0.14	2.25±0.11	2.59±0.10
PPN	2.79±0.15	3.17±0.32	2.90±0.09

Changes in OD ratio between the parkinsonian side of the brain in the unilateral animals and the equivalent structure in the parkinsonian animals which received dopamine agonists have been compared using *t* tests (*$P < 0.05$, **$P < 0.01$) CD = caudate nucleus, PUT = putamen; GPL = lateral segment of the globus pallidus; STN = subthalamic nucleus; STN-V = ventral portion of the subthalamic nucleus; GPM = medial segment of the globus pallidus; VA-VL = ventral anterior-ventral lateral complex of the thalamus, SN = substantia nigra; PPN = pedunculopontine nucleus.

As can be seen in Table 2, administration of a dopamine agonist had a significant effect on 2-DG uptake in the subthalamic nucleus and the globus pallidus. Administration of a dopamine agonist resulted in a 46% increase in OD ratio in the parkinsonian subthalamic nucleus (*see* Table 2; parkinsonian side vs parkinsonian plus dopamine agonist). This increase in 2-DG uptake was not homogeneous. The ventral medial tip of the structure was more affected than the rest of the nucleus. This is illustrated in Fig. 1. When the densitometric analysis was restricted to the ventral half of the

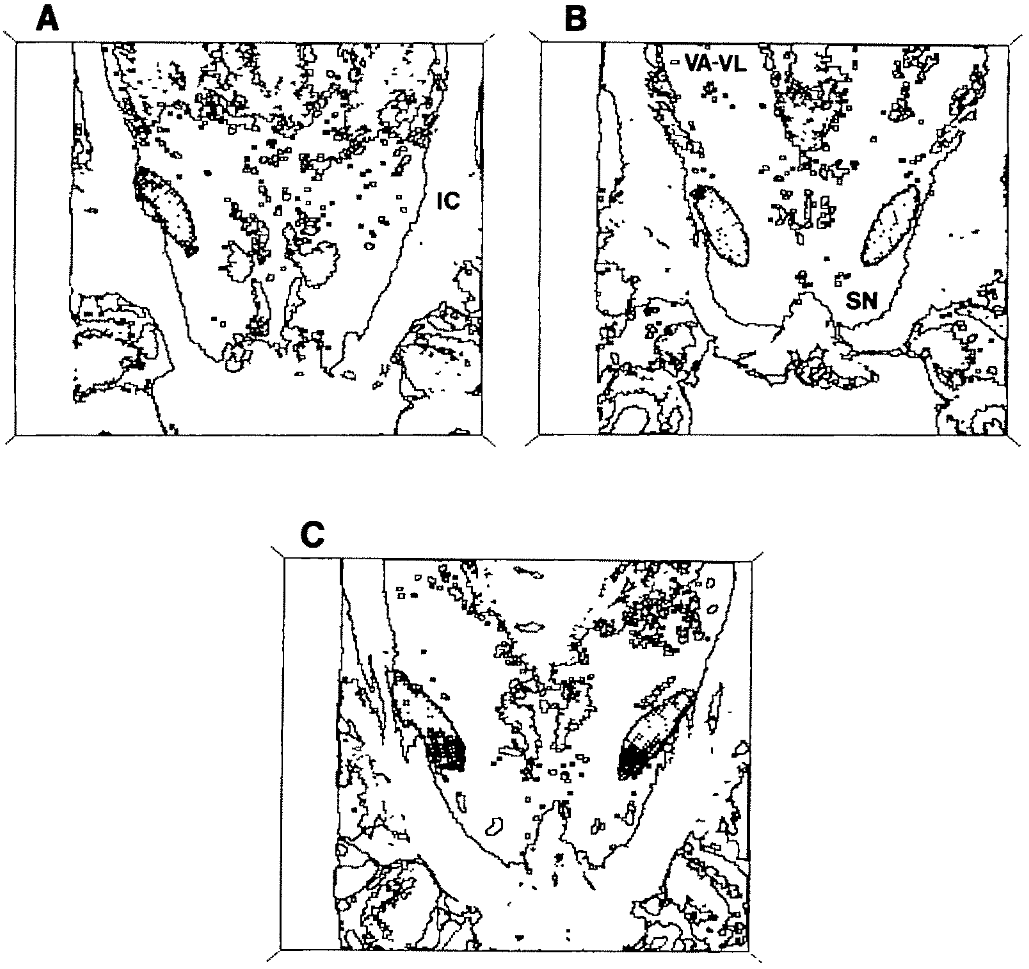

FIG. 1 Diagram showing the regional distribution of 2-DG uptake in the subthalamic nucleus of three animals. This figure is a printout of autoradiographs after they have been image analysed A threshold has been set which corresponds to a particular optical density. Only structures which are above this threshold, i.e. more optically dense, appear in the final image. A is from a unilateral parkinsonian animal which received no dopamine agonist. The stippled area shows the subthalamic nucleus on the non-lesioned side of the brain. The subthalamic nucleus ipsilateral to the injection of MPTP is paler than the threshold and therefore does not show up. B is from a parkinsonian animal which received a dopamine agonist but was not dyskinetic. The stippled area shows the subthalamic nucleus. C is from a parkinsonian animal which had peak-dose dyskinesia. The image has been produced using the same threshold parameters as used in B The threshold was then raised and a second image superimposed on top of the original The area of increased uptake, which is particularly noticeable in the medial tip of the dystonic subthalamic nucleus (area of heavy stipple), can be seen. Note, this threshold procedure allows comparisons of the regional distribution of label to be studied but does not permit quantitative cross-animal comparisons to be made. IC = internal capsule, VA-VL = ventral anterior-ventral lateral nuclei of the thalamus; SN = substantia nigra.

subthalamic nucleus a difference of 53% was found between the OD ratio of the parkinsonian animals which received the dopamine agonist and those which did not (parkinsonian side vs parkinsonian and dopamine agonist). It should be noted that this part of the analysis involved performing nine separate *t* tests. This large number of comparisons increases the probability of the results giving an apparently significant difference by chance alone. The results for the medial segment of the globus pallidus and the subthalamic nucleus, which were significant at the 5% level (*see* Table 2), must therefore be treated with some caution. Furthermore, the small size of the groups of animals makes the use of inferential statistics difficult. In order to overcome these difficulties the raw densitometric data are presented in an Appendix which enables the extent of overlap of the values from individual animals to be judged.

The data from the unilateral parkinsonian animals showed that, in the absence of a dopamine agonist, the subthalamic nucleus of the lesioned side was paler than the equivalent structure in the non-parkinsonian brain. Administration of the dopamine agonist reversed this situation by returning the OD ratio of the subthalamic nucleus to that seen in the non-parkinsonian brain. However, although not statistically significant, the administration of the agonist appeared to make the level of 2-DG uptake overshoot the values for the subthalamic nucleus in the normal brain.

Administration of a dopamine agonist to the parkinsonian brain also resulted in a significant increase in the OD ratio of the medial segment of the globus pallidus. This increase in label was not homogeneous. The precise pattern of increased uptake varied from animal to animal but was usually restricted to the lateral part of the medial segment and along its dorsal edge (*see* Fig. 2). The level of 2-DG uptake in the medial pallidal segment in the unilateral parkinsonian animal was higher on the lesioned side of the

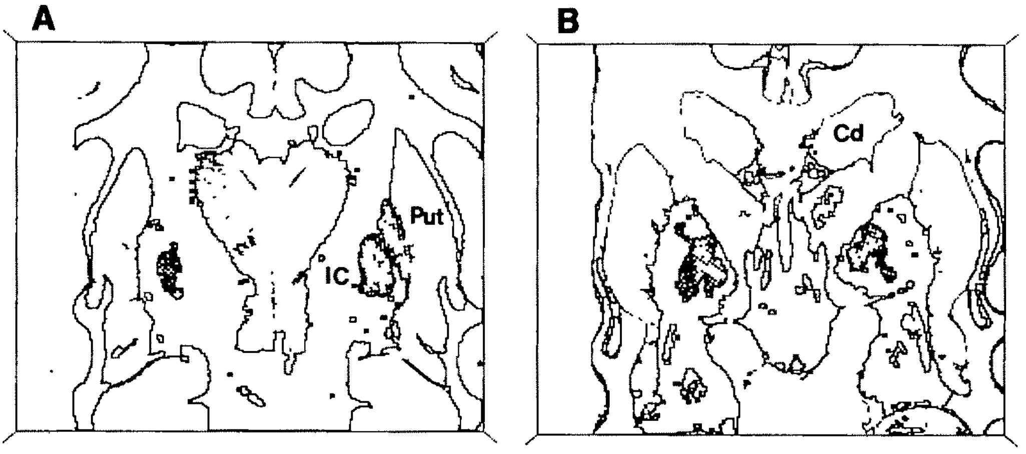

FIG. 2. Diagram showing the regional distribution of 2-DG uptake in the globus pallidus of two animals. This figure is a printout of autoradiographs after they have been image analysed using a threshold technique (*see* Fig. 1 for explanation) A is from a unilateral parkinsonian animal which did not receive a dopamine agonist. The side of the brain contralateral to the injection of MPTP (*left*) shows the medial segment of the globus pallidus as a stippled area The lateral segment of the globus pallidus is beneath the threshold (i e. too pale), and so does not appear in the image. On the right side of the brain, both the segments of the parkinsonian globus pallidus can be seen. B is from a parkinsonian animal which had peak-dose dystonia. The medial pallidal segment can be seen (stippled area), whereas the lateral pallidal segment is beneath the threshold. The pattern of uptake in the medial segment of the globus pallidus was not homogeneous. Strongest label can be seen along the lateral and dorsal borders of the structure. IC = internal capsule, Put = putamen, Cd = caudate nucleus.

brain than on the unlesioned side. Thus, the increase in 2-DG uptake in the parkinsonian medial pallidal segment following the administration of a dopamine agonist appeared to exacerbate this asymmetry in uptake rather than reduce it. In contrast, administration of a dopamine agonist to the parkinsonian brain appears to reduce the level of 2-DG uptake in the lateral pallidal segment to levels which are seen in the equivalent structure in the normal brain.

The pattern of uptake in the subthalamic nucleus and the globus pallidus appeared to be independent of the type or dose of dopamine agonist administered. No other significant changes in 2-DG uptake were seen though the VA-VL thalamic complex showed decreased levels of uptake following the administration of the dopamine agonist.

Uptake of 2-DG in dopamine-agonist induced dyskinesia. A significant difference in OD ratio of the subthalamic nucleus was found across the subgroups of parkinsonian animals that received a dopamine agonist (one-way ANOVA, F = 5.5, $P < 0.04$) (*see* Table 3). Multiple comparison tests revealed a significant difference in the OD ratio between the non-dyskinetic group and the peak-dose dystonic group. The results of the inferential statistical analysis are supported by the distribution of the OD ratios for the individual animals as shown in the Appendix of raw data. The individual OD ratios for each of the three non-dyskinetic animals are smaller than any of the ratios from those animals with peak-dose dyskinesia. Thus, the subthalamic nucleus from the peak-dose dystonic animals showed a 35% increase in the OD ratio compared with the value for the equivalent structure in the non-dyskinetic animals. A 22% increase in the peak-dose choreic group and the non-dyskinetic group was also seen but this was non-significant.

TABLE 3 THE PATTERN OF 2-DG UPTAKE IN ANIMALS WITH PEAK-DOSE DOPAMINE AGONIST-INDUCED DYSKINESIA

The dyskinetic animals have been divided into two groups on the basis of the nature of their dyskinesia. The dyskinesia in the first group of animals was predominantly choreic in nature whereas the dyskinesia in the second group of animals was mainly dystonic. Levels of 2-DG uptake in these animals were compared with levels in the non-dyskinesia animals (parkinsonian animals which were sacrificed on treatment but which showed no dyskinesia, i.e. clinically normal).

The results are expressed in terms of OD ratios. Numbers are means and standard errors.

	Non-dyskinetic (n = 3)	*Peak-dose chorea (n = 3)*	*Peak-dose dystonia (n = 3)*
CD	3.69±0.42	3.30±0.33	4.21±0.26
PUT	3.62±0.33	3.40±0.29	4.40±0.32
GPL	2.29±0.17	2.29±0.15	2.31±0.03
STN	3.48±0.27	4.26±0.33	4.70±0.16*
STN-V	3.79±0.18	5.11±0.32	5.15±0.23**,***
GPM	2.32±0.10	2.53±0.18	2.50±0.10
VA/VL	2.68±0.26	2.58±0.02	2.37±0.04
SN	2.70±0.12	2.27±0.08	2.81±0.81
PPN	3.00±0.11	2.80±0.39	2.88±0.10

Differences in OD ratio between the three groups have been assessed for each structure using one-way analysis of variance followed by the Tukey honestly significant differences multiple comparison test. *Non-dyskinetic vs dystonic, $P < 0.01$; **non-dyskinetic vs dystonic, $P < 0.01$, ***non-dyskinetic vs choreic, $P < 0.01$. For abbreviations, *see* Table 2.

When just the medial tip of the subthalamic nucleus was analysed, the OD ratios for both the peak-dose choreic group and peak-dose dystonic group were found to be significantly larger than the values for the equivalent non-parkinsonian structure (one-way ANOVA, $F = 9.7$, $P < 0.01$: multiple comparison test; non-parkinsonian side vs peak-dose chorea, $P < 0.02$; non-parkinsonian side vs peak-dose dystonia, $P < 0.01$).

No significant differences in the OD ratios for the medial pallidal segment between the non-dyskinetic, choreic and dystonic groups was found. However, qualitative differences between the groups could be seen (*see* Fig. 2). As stated previously, the pattern of 2-DG uptake in the medial pallidal segment was not homogeneous, the increase in label being concentrated in the lateral and dorsal parts of the structure. This pattern was most noticeable in the animals from the dystonic group. All three animals showed this pattern of uptake. In contrast only two of the choreic animals and one of the non-dyskinetic animals displayed this pattern.

The VA-VL thalamic complex in both the choreic and dystonic groups showed decreased 2-DG uptake compared with that seen in the non-dyskinetic animals. However, significant differences were not found between the OD ratios of the VA-VL thalamus in either of the dyskinetic groups and the non-dyskinetic group.

DISCUSSION

Effect of dopamine agonists on 2-DG uptake in the parkinsonian brain

Administration of a dopamine agonist had a striking effect on 2-DG uptake in the parkinsonian brain. This was most apparent in the subthalamic nucleus.

Subthalamic nucleus. Administration of the dopamine agonist increased dramatically the uptake of 2-DG in the subthalamic nucleus of the parkinsonian brain irrespective of the degree of severity of the parkinsonism, the dose or type of dopamine agonist used or whether the animals developed peak-dose dyskinesia or not. This may be predicted since the parkinsonian subthalamic nucleus shows decreased levels of 2-DG uptake relative to the equivalent structure in the normal brain (Mitchell *et al.*, 1989*b*). However, the administration of the dopamine agonist did not simply return the levels of 2-DG uptake to normal values, but rather it resulted in abnormally high levels of 2-DG uptake compared with that seen in the subthalamic nucleus of non-parkinsonian brains. This increase in label was not uniform across the structure but was greatest in the ventromedial tip.

Neural tissue has many requirements for glucose, thus making it difficult to interpret the underlying causes of patterns of 2-DG uptake. It is known, however, that the change in the pattern of labelling that results from an experimental manipulation primarily reflects changes in the 2-DG uptake in terminals rather than pericarya (Schwartz *et al.*, 1979; Mata *et al.*, 1980; Auker *et al.*, 1983). A change in the level of 2-DG uptake in a structure might therefore reasonably be assumed to be due to changes in the presynaptic activity of its afferent inputs or intrinsic synaptic interactions.

Regarding afferent inputs to the subthalamic nucleus there are three possible candidates. First, the lateral segment of the globus pallidus is known to send a topographically organized projection to the subthalamic nucleus (Kim *et al.*, 1976; Carpenter *et al.*, 1981*a*,*b*). Interestingly, in the rodent, the part of the pallidal complex which appears to project most strongly to the medial tip of the subthalamic nucleus is the ventral pallidum

(Zahm, 1989). This region has been implicated as part of an anatomical circuit which mediates orofacial dyskinesia in the cat (Cools *et al.*, 1989). Secondly, the medial tip of the rodent subthalamic nucleus receives a cortical input from the cingulate gyrus (Canteras *et al.*, 1990). Thirdly, the ventral striatum or nucleus accumbens projects directly to the medial tip of the subthalamic nucleus in the rat (Groenewegen and Russchen, 1984; Groenewegen and Berendse, 1990) and the primate (Powell and Leman, 1976). This third input is the most attractive possibility since the ventral striatum is known to play an important role in controlling locomotor responses to dopamine agonists such as amphetamine and apomorphine (Costall *et al.*, 1977; Mogenson and Wu, 1986).

Lateral segment of the globus pallidus. The levels of 2-DG uptake in the lateral pallidal segment returned towards normal values following the administration of a dopamine agonist to the parkinsonian monkey. This might be predicted since the dopamine agonist reverses the parkinsonism. However, we have previously reported that a unilaterally parkinsonian animal which had unilateral dopamine agonist-induced dystonia showed increased uptake in the lateral pallidal segment of the dystonic brain when compared with the equivalent structure on the non-parkinsonian side of the brain (Mitchell *et al.*, 1990). This suggests that dopamine agonists have an even greater effect on reducing 2-DG uptake in the non-parkinsonian lateral pallidal segment than in the parkinsonian lateral pallidal segment.

The most likely explanation for the decrease in 2-DG uptake in the lateral pallidal segment seen in the experiment reported here would be a decrease in the synaptic activity in the output cells of the putamen. This structure is known to send a massive topographically organized, GABAergic/enkephalinergic input to the lateral pallidal segment (Nagy *et al.*, 1978; Haber and Elde, 1981, 1982). We have studied the activity of these enkephalinergic cells using *in situ* hybridization techniques in an attempt to confirm the 2-DG finding. To this end we have demonstrated that the striatum of the parkinsonian macaque shows increased levels of enkephalin mRNA expression (Augood *et al.*, 1989). This increase in expression is not homogeneous but it has a gradient such that the ventrolateral putamen shows the largest increase in expression and the dorsomedial striatum shows the least. The same procedure was applied to sections of striatum from one of the animals in this study, CYN 143. This animal was hemi-parkinsonian and developed dopamine agonist-induced dystonia. The pattern of label seen in this animal was different to that seen in the parkinsonian brain in that there was a reduction of label in the ventrolateral putamen (i.e. the striatal area which had shown the greatest levels of expression in the parkinsonian condition) (Frayne *et al.*, 1992). This observation implies that the striatal cells which project to the lateral pallidal segment are over-active in the parkinsonian state but begin to return to normal values when treated with a dopamine agonist.

Medial segment of the globus pallidus. The medial segment of the globus pallidus in the parkinsonian animals which received a dopamine agonist showed higher levels of 2-DG uptake than those not receiving the drug. This was an unexpected finding for two reasons. First, the parkinsonian medial pallidal segment shows slightly higher levels of 2-DG uptake than the equivalent structure in the non-parkinsonian brain. One would therefore predict that administration of a drug which reversed the parkinsonian features would result in decreased levels of 2-DG uptake. Secondly, we know from previous 2-DG studies that the medial pallidal segment shows decreased uptake of 2-DG in animals with experimental chorea and experimental ballism (Mitchell *et al.*, 1985*b*,*c*, 1989*a*). Thus, hyperkinetic disorders appear to be characterized by decreased levels of 2-DG uptake. Since some of the animals which received the dopamine agonist became dyskinetic one would predict that they would show decreased levels of 2-DG uptake.

The increased uptake of 2-DG seen in the medial pallidal segment of these animals is most likely due to increased terminal activity of an afferent input. The two main projections to the structure come from the subthalamic nucleus and the striatum (Kim *et al.*, 1976; Carpenter *et al.*, 1981*a*,*b*; Haber and Elde, 1981, 1982), which use an excitatory amino acid and GABA/substance P as their respective transmitters.

Effects of dopamine agonist-induced dyskinesia on 2-DG uptake

The subthalamic nucleus of the dyskinetic animals showed much higher levels of 2-DG uptake, especially in the ventral medial tip, than that seen in the clinically normal animals. This implies that abnormal activity in the subthalamic nucleus, and possibly its ventromedial portion in particular, underlies the mediation of dopamine agonist-induced dyskinesia. As suggested above, this pattern of activity may reflect increased activity in the projection to the subthalamic nucleus from the lateral pallidal segment. If this were the case, it would be predicted that the lateral pallidal segment would also show a different pattern of label in the dyskinetic and non-dyskinetic groups. Although this was not detected, all animals exposed to dopamine agonist showed decreased uptake of 2-DG in the lateral segment of the globus pallidus, consistent with decreased striatopallidal activity and increased activity of the inhibitory projection from the lateral pallidal segment to the subthalamic nucleus. If the increase in label in the subthalamic nucleus of the dyskinetic brain was due to increased synaptic activity of the input from the cerebral cortex, the nucleus would become overactive since the transmitter in this pathway is thought to be an excitatory amino acid (Cotman *et al.*, 1988). It is deemed unlikely that the subthalamic nucleus is overactive in dopamine agonist-induced movement disorders in view of previous experiments which have demonstrated that the subthalamic nucleus is underactive in dyskinesia elicited by a variety of experimental approaches (Carpenter *et al.*, 1950; Mitchell *et al.*, 1985*b*,*c*, 1989*a*, 1991). It is possible that the increase in label seen in the ventral tip of the dyskinetic subthalamic nucleus is due to increased terminal activity in the projection from the ventral pallidum or ventral striatum. These pathways probably utilize GABA as its transmitter. Increased GABAergic transmission would therefore be expected to result in increased inhibition of the subthalamic nucleus.

The medial pallidal segment showed an increase in 2-DG uptake in the dyskinetic animals compared with the non-dyskinetic group. The two main afferents projections to the medial pallidal segment originate from the subthalamic nucleus and the striatum (Kim *et al.*, 1976; Carpenter *et al.*, 1981*a*,*b*; Haber and Elde, 1981, 1982). Since, as discussed above, we believe the subthalamic nucleus to be underactive in dyskinesias the increase in label seen in the medial pallidal segment of these animals is best attributed to increased activity in the GABAergic/substance P projection from striatum.

The pattern of increased label in the medial segment of the globus pallidus was heterogeneous as noted above, the label being densest on the dorsomedial border of the structure. This pattern of label did not, however, show a precise correspondence to the pattern of termination of either the striatal or subthalamic inputs to the medial pallidal segment (Carpenter *et al.*, 1981*a*,*b*; Parent and Smith, 1987).

Relationship between peak-dose chorea and peak-dose dystonia

The level of 2-DG uptake in the subthalamic nucleus was increased in the dyskinetic compared with the non-dyskinetic animals as discussed above. The size of the increase appeared to be dependent upon the type of dyskinesia present, the subthalamic nucleus from the dystonic animals showing a greater increase than the equivalent structure in the choreic animals. This suggests that there is greater inhibition of the subthalamic nucleus in dystonia than chorea.

Neural mechanism underlying dopamine agonist-induced dyskinesia

Dopamine agonist-induced dyskinesia is characterized by increased uptake of 2-DG in the subthalamic nucleus which is particularly apparent in the ventromedial part of the structure. This increase in uptake may reflect increased activity in the GABAergic pathway to the subthalamic nucleus from the ventral striatum and/or ventral pallidum. This overactivity would result in decreased subthalamic firing. The decreased output of the excitatory amino acid efferents of the subthalamic nucleus may combine with increased activity of the putaminal cells which project directly to the medial pallidal segment resulting in decreased activity of this structure. Decreased activity in the medial pallidal segment would in turn result in the loss of GABAergic inhibition of the VA-VL thalamus which would become overactive. Thus, the evidence presented supports the hypothesis that dopamine agonist-induced dyskinesia in parkinsonism is associated with decreased activity of the subthalamic nucleus and medial pallidal segment. Thus dopamine agonist-induced dyskinesia shares a common neural mechanism with other forms of chorea and with ballism (Mitchell *et al.*, 1985*c*, 1989*a*). The data further suggest that dopamine-induced dystonia may be associated with even greater reductions of activity in the medial segment of the globus pallidus than in chorea.

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APPENDIX

Raw data obtained from the densitometric analysis of all autoradiographs. The results are expressed in terms of OD ratios

Animal	*CD*	*PUT*	*GPL*	*STN*	*STN-V*	*GPM*	*VA-VL*	*SN*	*PPN*
Non-dyskinetic									
CYN 159	3.64	3.69	2.63	3.71	3.88	2.51	2.70	2.47	3.20
CYN 154	2.99	3.01	2.09	2.94	3.45	2.15	2.21	2.79	2.82
CYN 170	4.45	4.15	2.15	3.79	4.05	2.29	3.12	2.84	2.97

APPENDIX (*continued*)

Animal	*CD*	*PUT*	*GPL*	*STN*	*STN-V*	*GPM*	*VA-VL*	*SN*	*PPN*
Peak-dose chorea									
CYN 112	2.86	2.96	2.16	3.87	5.20	2.47	2.56	2.33	2.41
CYN 116	3.09	3.31	2.13	4.00	4.52	2.24	2.56	2.10	*
CYN 113	3.94	3.94	2.59	4.91	5.60	2.88	2.63	2.37	3.18
Peak-dose dystonia									
CYN 156	4.01	4.05	2.24	4.47	4.71	2.34	2.34	2.65	3.06
CYN 114	3.91	4.11	2.36	4.62	5.25	2.49	2.41	2.89	2.73
CYN 143	4.72	5.04	2.32	5.01	5.49	2.67	2.37	2.90	2.85
Unilateral parkinsonian; parkinsonian side									
26	3.99	4.02	2.50	2.39	2.53	1.95	2.37	2.02	2.81
27	4.45	4.58	2.81	3.28	3.38	2.30	2.95	2.38	3.82
34	4.15	4.20	2.82	2.94	3.22	2.17	2.95	2.35	2.89
Unilateral parkinsonian; non-parkinsonian side									
26	3.86	3.73	1.85	2.60	2.82	1.88	2.13	2.03	2.59
27	3.90	4.00	2.22	3.65	3.81	2.24	2.67	2.38	3.08
34	4.03	3.98	2.34	3.30	3.53	2.25	2.79	2.48	2.71

*Data unavailable. CD = caudate nucleus; PUT = putamen; GPL = lateral segment of the globus pallidus; STN = subthalamic nucleus; STN-V = ventral portion of the subthalamic nucleus; GPM = medial segment of the globus pallidus; VA-VL = ventral anterior-ventral lateral complex of the thalamus; SN = substantia nigra; PPN = pedunculopontine nucleus.

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BEHAVIOURAL ANALYSIS OF UNILATERAL MONOAMINE DEPLETION IN THE MARMOSET

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SUMMARY

Unilateral stereotaxic injections of 6-hydroxydopamine (6-OHDA) into the nigrostriatal bundle of marmosets (*Callithrix jacchus*) produced substantial losses of tyrosine hydroxylase immunoreactive neurons from the substantia nigra, and mean dopamine (DA) depletions of 98–99% in the caudate nucleus, putamen and nucleus accumbens, and of 91–97% in frontal cortex, on the side of the lesion. Noradrenaline (NA) and 5-hydroxytryptamine (5-HT) levels were also affected. Behavioural tests conducted pre-operatively and at regular intervals during the 6 mths following surgery revealed persistent deficits in the lesioned marmosets as a group compared with sham-lesioned controls, although individual marmosets sometimes recovered or showed no initial deficit on some tests. The main behavioural effects of the lesion were as follows: (i) an increase in the time spent with the head positioned ipsilaterally with respect to the rest of the body; (ii) ipsilateral spontaneous and amphetamine-induced rotation, although occasional intermittent periods of contralateral rotation and head biases were also recorded; (iii) contralateral apomorphine-induced rotation; (iv) reduced spontaneous activity; (v) ipsilateral hand preference on a conveyor belt task, although hand skill (measured as percentage errors when the speed of the belt was increased) was not affected; (vi) neglect of contralateral stimuli, both at the conveyor belt where lesioned monkeys often failed to respond on trials on which apple pieces arrived from the contralateral side, and on a test of sensorimotor neglect in which adhesive labels were placed around both feet. Comparisons of biochemical measures of the lesion with behavioural scores in individual monkeys suggest that DA depletions in excess of 95% are essential for long-term behavioural deficits.

INTRODUCTION

Lesions which deplete the striatum of dopamine (DA) in experimental animals can produce behavioural deficits analogous to the symptoms of Parkinson's disease which may last for many months or even years (Schultz, 1982). However, not every animal which receives such a lesion will continue to show behavioural deficits over such a long period. Indeed, some lesioned animals may show no overt behavioural change at any time after surgery. The various compensatory processes which underlie recovery of function have been well documented and include both pre- and post-synaptic changes (Stricker and Zigmond, 1976; Zigmond and Stricker, 1989; Robinson *et al.*, 1990). The existence of these processes presents a practical problem for studies using animal models to assess potential therapies for Parkinson's disease since spontaneous recovery may confound any benefits due to the treatment under investigation. This is particularly true for studies examining the effects of tissue transplantation into the dopamine-depleted striatum.

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Transplants may take several weeks or months to become established and functionally effective in the host brain (Dunnett *et al.*, 1983*a*), giving ample time for any spontaneous recovery to occur. The experiment described here is part of a project which aims to develop a primate model of Parkinson's disease in the marmoset (*Callithrix jacchus*), a small New World monkey, suitable for assessing dopaminergic graft function. The specific aims of the study were (i) to produce a lesion which reliably reduced DA to levels likely to limit spontaneous recovery; (ii) to develop a range of behavioural measures which could be used to quantify lesion-induced impairments at regular intervals over a period of months; (iii) to examine the relationships between the severity and duration of different behavioural impairments and between the extent of the lesion assessed using biochemical measures of DA levels in the striatum and histological meaures of DA cell loss from the substantia nigra.

There have been surprisingly few studies of the behavioural effects of 6-hydroxydopamine (6-OHDA) lesions in monkeys (Schultz, 1982; Crossman, 1987), although long-term behavioural deficits following unilateral 6-OHDA lesions in marmosets have been reported (Crossman and Sambrook, 1978; Sambrook *et al.*, 1979). The most widely used tool for producing experimental parkinsonism in primates is 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Schultz, 1988; Jenner, 1989), but the pronounced variability between individuals of the same species in their susceptibility to the toxin and the high probability of some spontaneous behavioural recovery (Eidelberg *et al.*, 1986; Elsworth *et al.*, 1987, 1989) is a considerable disadvantage for studies attempting to assess dopaminergic graft function (Dunnett and Annett, 1991). In contrast, spontaneous behavioural recovery is apparently less of a problem in studies using 6-OHDA to destroy dopamine pathways in rats, perhaps due to the greater consistency that is observed in the extent of dopamine depletion between animals. It is possible that 6-OHDA lesions in monkeys might produce more reliable and stable behavioural deficits than MPTP if, for example, the sites of the sterotaxic injections of 6-OHDA were such that dopamine was depleted from the nucleus accumbens as well as from the caudate nucleus and putamen, thus removing one of the possible mechanisms of recovery (Rose *et al.*, 1989; Jenner and Marsden, 1988). Alternatively, differences in the stability of behavioural effects of 6-OHDA lesioned rats compared with MPTP lesioned monkeys may be more apparent than real: experiments using rats are more likely to use rotation tests to screen and discard those animals which do not show profound lesion-induced behavioural deficits, and presumably do not have complete DA lesions, whereas experiments using monkeys usually use only a few animals such that the number of subjects is typically at a premium. In the present study we have used 6-OHDA rather than MPTP, primarily because the main aim was to produce reliable and stable behavioural deficits. However, this choice also eliminates the safety hazards of working with MPTP (Yang *et al.*, 1988).

An important goal of the present experiment was to design a range of behavioural measures for quantifying the lesion-induced deficits. If there is any recovery over time then comparisons between measures will show whether all impairments recover at the same rate and to the same extent, or whether some are more stable and sensitive than others, making them more useful indices of lesion damage and recovery. The inclusion of a range of measures is also important with respect to the potential use of the model in assessing dopaminergic graft function. The most sensitive and widely used test of graft function in unilaterally lesioned rats is the abolition of drug-induced rotation. However, not all behaviours disrupted by a dopaminergic lesion are restored by dopaminergic grafts, notably aphagia and adipsia in the bilaterally lesioned animal (Dunnett *et al.*, 1983*b*), skilled use of the paw contralateral to a unilateral lesion (Dunnett *et al.*, 1987) and the exploratory and hoarding behaviours disrupted by dopamine depletion from the nucleus accumbens (Herman *et al.*, 1988). A primate model which includes several behavioural measures could provide more information relevant to the extent of recovery which might be achieved with such grafts in parkinsonian patients. A preliminary report of a subset of these behavioural tasks on some of the marmosets (L4-L7 and S11-S14) has been presented elsewhere (Annett *et al.*, 1990).

METHODS

Subjects

Six female and seven male marmosets, aged 18–30 mths and weighing 300–380 g each, were used. They were housed in pairs, normally two lesioned or two sham injected animals together, in a colony room illuminated by natural daylight. The daily meal of fruit, bread and chow was given during the late afternoon after behavioural testing had been completed. Food restriction was not necessary for the animals to perform the required tasks.

Surgery

Surgery was carried out under Saffan (0.4 ml of 12 mg/ml solution; Glaxo Vet Ltd, Uxbridge, UK) anaesthesia and aseptic conditions. 6-Hydroxydopamine [4 mg/ml free base weight 6-OHDA HBr (Sigma, Poole, Dorset, UK), dissolved in 0.01% ascorbate-saline] was injected stereotactically into five sites within the nigrostriatal bundle on one side of the brain (coordinates: AP+6.5; L±1.2, V+6, V+7; L±2.2, V+6.5, V+7.5; L±3.2, V+7.5; Stephan *et al.*, 1980). Three microlitres were injected into the most lateral sites and 2 μl into each of the four other sites. Seven (lesion) marmosets received these injections of 6-OHDA, while the other six (control) monkeys underwent the same procedure, except that the ascorbate vehicle was injected rather than the toxin. The allocation of monkeys to the two groups and the side of the toxin or vehicle injections was balanced so that the groups were matched with respect to their pre-operative conveyor belt scores (*see below*).

Behavioural tests

Position of the head. Each monkey was observed in the home cage and the position of the head with respect to the rest of the body (i.e. right, left or straight ahead) was recorded every second for 60 s following the beat of a metronome (*cf* Scraggs and Ridley, 1978). Readings were obtained from each animal in turn. The process was then repeated twice to give a total observation period of 3 min per monkey on a given test day. Pre-operative readings were taken on two test days and post-operative readings on four test days most weeks during the 6 mths of the experiment. All readings were made by the same observer. Duplicate readings were made by a second blind observer over 3 d at approximately 20 d post-operatively, and yielded a high level of inter-rater reliability (Spearman's rho: 0.96, 0.98, 0.93 on the 3 days).

Rotation. Rotation was recorded by filming the marmosets for 30 min while in a transparent Perspex box (as used with the conveyor belt apparatus). The recording was made on 'long-play' and then replayed on 'fast forward' so that the number of complete 360° turns made during the half-hour could be counted in only a couple of minutes. Rotation following an i.m. injection of 0.5 mg/kg *d*-amphetamine sulphate (Sigma, Poole, Dorset, UK; dissolved in 0.9% sodium chloride) 30 min prior to the start of the test was recorded once a month on months 2–6 post-operatively. Spontaneous rotations were recorded every week throughout the experiment, excluding those weeks in which the monkeys had received amphetamine. Rotations in response to a series of doses of apomorphine HCl (Sigma, Poole, Dorset, UK) were recorded at 8 mths post-operatively. Doses of 0.0 (ascorbate-saline vehicle), 0.05, 0.1 or 0.5 mg/kg were injected i m., 30 min before the start of the test, in a counterbalanced order and with at least 2 d between injections.

Activity cage. A standard home cage (70×50×62 cm) situated in the main colony room was modified to incorporate nine infra-red photocell beams which ran parallel to the front of the cage. One beam was positioned 4 cm above each of the two wooden perches (perches at height×depth, 19×17 cm and 44×42 cm). Four beams ran 4 cm above the floor at depths of 4 cm, 20 cm, 36 cm and 52 cm from the front of the cage. Three further beams were positioned 4 cm from the front at 20 cm, 36 cm and 52 cm above the floor. Interruptions of the beams were counted on-line by a microprocessor which distinguished between repetitions (same beam broken as on the previous count) and locomotor counts (different beam broken).

Spontaneous activity counts over 90 min commencing as soon as the animal was placed in the cage were collected in a single test conducted approximately 7 mths post-lesion. Activity in response to doses of 0, 0.05, 0.1 and 0.5 mg/kg apomorphine was recorded in conjunction with the rotation tests described above. Thus, from 0–30 min and 60–90 min post-injection the monkey was placed in the photocell cage, while rotations were recorded during the intervening 30–60 min. Finally, activity was recorded for 90 min immediately following an i.m. injection of 0.5 mg/kg amphetamine or saline. All activity tests were conducted during daylight hours, normally between 11.00 h and 16.00 h.

Conveyor belt: apparatus. The conveyor belt apparatus was identical to that used by Evenden and Robbins (1984) for testing rats except that the rear was modified to hold a Perspex test box (23×15.5×17 cm) in which a marmoset was brought from the home cage and remained while performing the task. The conveyor belt at the front of the apparatus could be seen by the monkey through a 15×10 cm opening 9 cm above the floor of the test box. Access to the belt was restricted by a wire grid which was positioned so as to leave a gap 2 cm high at the level of the belt surface. Clear Perspex baffles at each end restricted the width of the gap to 6 cm. The moving surface of the belt was 3 cm wide, with flat aluminium sills, 0.5 cm wide, on either side. A 12.5 V electric motor powered the belt which could move at variable speeds and reverse direction by means of an adjustable transformer. The speed of the belt was normally set at 8 cm/s. At the start of each trial a cube of apple (approximately 3 mm^3) was placed on the end of the stationary belt by the experimenter who sat in front of the apparatus. When the belt was switched on the piece of apple took about 2 s to reach the gap through which the monkey was free to respond. A 40 W standard lamp above the test box illuminated the apparatus. Testing was carried out with the room lights off. A smoked Perspex screen fixed to the front of the apparatus prevented the monkey from seeing the experimenter.

Conveyor belt: training and testing. The marmosets were trained pre-operatively to take pieces of apple from the moving belt. The training comprised initial familiarization to the Perspex test box in the home cage, followed by sessions in the conveyor belt apparatus in which pieces of apple were placed on the stationary belt. Once the monkey had learned to take the stationary apple pieces promptly, trials with moving pieces of apple commenced. Now the monkey had to reach and grasp the apple pieces quickly as they passed the gap. If the piece of apple was not picked up as it went past it continued beyond the gap out of reach. Training continued until 50 trials were consistently completed within a 10–20 min session. Altogether, this pre-operative training took approximately 2–4 wks of daily sessions.

Pre-operative testing comprised blocks of 100 trials (50 trials on two consecutive days) of reaching for both stationary and moving apple pieces. On 'stationary' trials the Perspex baffles were positioned so as to close completely the gap through which the monkeys had been trained to reach. The apple piece was brought into position in the centre of the belt, arriving from the monkey's right on the first 50 trials and from the left on the next 50 trials, and after 2 s one of the baffles was moved so as to reopen the gap. The apple piece was left in place until the monkey responded. The hand used to make the response was recorded. A session of 50 trials continued until the apple pieces had been taken or 30 min had elapsed. On 'moving' trials apple pieces arrived from either the right or the left in a pseudo-random order (Gellermann, 1933). The experimenter recorded whether an attempt was made to retrieve the apple pieces (defined as any reach through the gap while the belt was moving) and the hand used in the attempt. The outcome of each trial was recorded onto one of four mutually exclusive categories. (i) *Success*: the monkey reaches and retrieves the apple piece. (ii) *Fail*: the monkey reaches and touches the apple piece, but does not retrieve it. (iii) *Miss*: the monkey reaches through the gap but does not touch the apple piece. (iv) *No response*: the monkey makes no reaching attempt. Trials continued at a steady pace of approximately one every 7 s, provided the monkey was either facing the belt or sitting directly next to it, the next trial starting as soon as the apple piece from the previous trial had been eaten. Each monkey was tested over two blocks of stationary and two blocks of moving trials before going on to surgery.

Post-operative testing commenced 6 d after surgery with two blocks of stationary followed by two blocks of moving trials. Five further blocks of stationary and moving trials were given during the first 2 mths after surgery. Thereafter, during months 3–6, blocks of moving trials were given once every 2 wks, and a block of stationary trials once a month.

A series of moving conveyor belt trials in which the speed of the belt was increased from 8 to 26.4 cm/s, in 4.6 cm/s steps over consecutive blocks of 100 trials (i.e. two test days at each of the five speeds), followed by a final block of 100 trials at 8 cm/s, was given at approximately 7 mths post-operatively.

In a further test of lesion-induced neglect (*see below* adhesive label test) seven pieces of apple were placed 2 cm apart in a row on the stationary belt. The Perspex baffles, initially closed, were opened so as to allow access only to the centremost piece of apple. As soon as the monkey had taken this piece the baffles were opened completely and the order and latencies in which the remaining six pieces were taken were recorded. The test was repeated five times on each of two daily sessions.

Adhesive labels. In order to assess sensorimotor neglect, the adhesive label test designed by Schallert *et al.* (1982) for rats was modified for use with marmosets. Identical adhesive labels were placed bilaterally around the feet. Marmosets will normally use their teeth to remove such labels within a couple of minutes. The monkeys were held in a small restraining device (Hearn, 1977) while the labels (Self Adhesive Address Labels, Ryman), previously cut to 2×6.5 cm, were placed completely around each foot between the ankle and the little toe with the overlap towards the inside. A trial started as soon as the monkey was returned to the home cage (the cage mate having been temporarily removed). The latencies to contact (defined as the first bite) and remove (at least three-quarters removed, including that on the underside of the foot) each label were recorded on six trials every month, each trial lasting until both labels had been removed or to a maximum of 10 min. In order to limit habituation to the labels, only two trials were given daily, normally on three consecutive days. On the 5th mth test, the labels were placed and the latencies were recorded by an observer who was unaware of the side of the lesion.

After the 6 mths of bilateral tests had been completed the latencies to contact and remove unilateral and bilaterally placed labels were compared. Four trials each were given of (i) one label around the ipsilateral foot only, (ii) one label around the contralateral foot only, and (iii) one label around the ipsilateral foot and another around the contralateral foot at the same time. The order of the trials was balanced, no more than three trials being given per test day.

Following the extinction procedure of Schallert *et al.* (1982), the impact of the relative sizes of the labels on the ipsilateral and contralateral feet was examined in the last test using adhesive labels. On each trial the width of the label around the ipsilateral foot was either three-quarters, one-half or one-quarter the width of that on the contralateral foot, the latter being of an identical size to labels used in previous tests. Three trials were given at each of the widths in a counterbalanced order.

Biochemistry and histology

On completion of the behavioural tests 9 mths after surgery the monkeys were killed by a barbiturate overdose and the brains rapidly removed. The forebrain was cut into coronal slabs 1–2 mm thick and dissected on ice to provide a series of tissue samples from striatal, cortical and hypothalamic sites (Table 1). The origins of the samples and transmitters assayed were as follows: coronal slab 1 (i.e. the first slab which passed through the striatum), anterior caudate (DA), nucleus accumbens (DA) and frontal cortex [noradrenaline (NA)]; coronal slab 2, mid-caudate (DA), anterior putamen (DA) and pre-optic area (NA); coronal slab 3, posterior caudate [DA and 5-hydroxytryptamine (5-HT)], posterior putamen (DA and 5-HT); parietal cortex (NA) and hypothalamus (NA). The dorsolateral, medial and orbital frontal cortex samples (DA), and the occipital and cerebellar samples (NA), were dissected directly from the surface of the brain. The samples were rapidly frozen on dry ice and then stored at 70°C for subsequent biochemical analysis by high performance liquid chromatography (HPLC) with electrochemical detection (Mefford, 1981).

The half of the brain caudal to the infundibulum was immersed for at least 7 d in Bouin's fixative prior to wax embedding and sectioning for histological analysis. Parallel series of 8 μm sections were mounted on glass slides and dewaxed prior to tissue processing. Alternative series were processed with the following stains: (i) Nissl staining with cresyl violet to visualize cell bodies; (ii) Masson-Fontana stain to visualize neuromelanin (Rális *et al.*, 1973), counterstained with neutral red; (iii) Palmgren silver stain to visualize nerve fibres (Rális *et al.*, 1973); (iv) immunocytochemical visualization of catecholamine-synthesizing neurons using a commercial polyclonal antibody raised in rabbits against tyrosine hydroxylase (TH; Eugene Tech, Allendale, NJ, USA). The sections were washed in Tris buffered saline, pH 7.6, and incubated overnight (16–24 h) at room temperature in primary antibody (1 : 200). The sections were then washed and incubated in a goat anti-rabbit secondary antibody (1 : 30; Sigma, Poole, Dorset, UK) for 2 h, washed, and incubated in rabbit peroxidase-anti-peroxidase (1 : 30; DAKO Ltd, High Wycombe, Bucks, UK) for 2 h. Immunoreactivity was visualized with the chromogen diaminobenzidine containing 0.03% hydrogen peroxide.

Statistics

Analyses of variance (ANOVAs) were used to make statistical comparisons between groups and conditions with *a posteriori* comparisons by *t* tests using the standard error of measurements derived from the relevant interaction term of the ANOVA. Square-root transforms were performed on data (indicated in the text) which did not initially satisfy the assumptions of normality and homogeneity of variance required for a parametric ANOVA. Data expressed as percentiles or a proportion of total trial time (e.g. position of the head, latency to contact or remove labels) were subjected to arcsine transformations prior to analysis (Mather, 1965).

RESULTS

Histology

Good coronal sections and staining were collected from the brains of six of the seven lesioned monkeys and four of the six controls. The final lesioned monkey was blocked so that a part of the substantia nigra was lost. In the fifth control monkey the brainstem block was cut horizontally, and although good staining was obtained, the different plane made comparison with the other cases difficult. The sixth control did not fix well and sectioned poorly so that no good sections were collected. Primary histological analysis was conducted on the TH immunostained sections, with the other stains employed for additional observation and confirmation.

Tyrosine hydroxylase immunoreactivity was clearly observed and unambiguous in large neurons throughout the substantia nigra region of the ventral mesencephalon (Fig. 1A,B). The distribution of TH immunoreactive (THir) cells in the pars compacta of the substantia nigra is illustrated for the intact side of one of the lesioned monkeys in Figs 1A and 2, and was fully compatible with previous descriptions based on catecholamine histofluorescence (Schofield and Dixson, 1982) and TH immunohistochemistry (Waters *et al.*, 1987). The cells of the substantia nigra pars compacta were equally clear in the Nissl material as large neurons with large rounded nuclei and relatively dense cytoplasm. The Masson-Fontana stain for neuromelanin revealed scattered silver grains in the majority, but not all neurons of the pars compacta which were particularly clear under dark field illumination.

The main ascending nigrostriatal bundle courses rostrally in the medial forebrain bundle over the subthalamic nucleus towards more rostral targets in the basal ganglia. However, in contrast to rodents, the ascending fibres start fanning out laterally towards the putamen via the globus pallidus at the level of the most rostral cells of the substantia nigra itself. As a consequence we needed to make several injection deposits of 6-OHDA placed in a medio-lateral direction just rostral to the nigra in order to achieve extensive lesions of this fibre tract. The site of the lesions could be determined by slight gliosis along the needle tracks at the site of the injection (Fig. 2). However, the injections caused no disturbance of the neuropil and healthy neurons could be observed in the Nissl stained sections close to the site of the injection. The lesions were associated with a virtually complete loss of THir neurons in the substantia nigra (Fig. 1C) and of THir fibres in

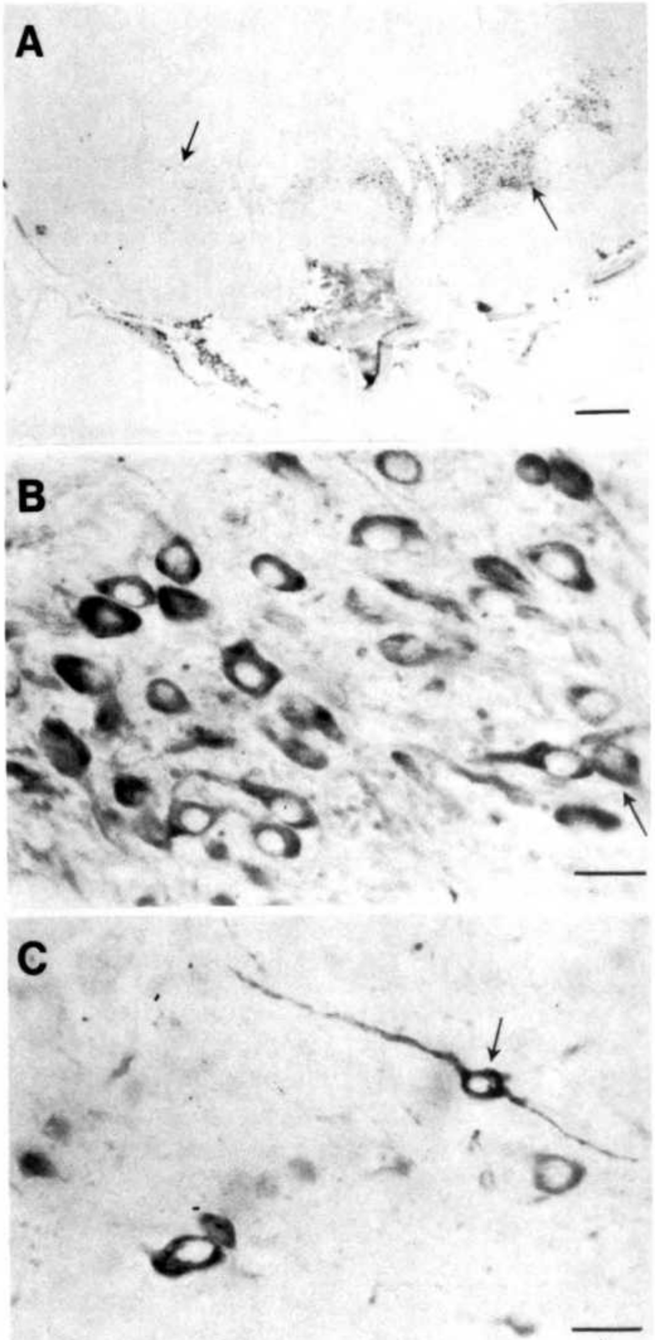

FIG. 1. A, low magnification of the intact (*right*) and lesioned (*left*) substantia nigra of monkey L6 stained with an antibody to tyrosine hydroxylase (TH). B, high magnification of individual immunoreactive (THir) staining neurons in the intact nigra in the region indicated by the arrow to the right in panel A. C, high magnification of the lesioned nigra in the region indicated by the arrow to the left in panel A. The loss of THir staining cells was virtually complete, but those cells which survived appeared to show an increased density of TH immunoreactivity. Scale bars: 200 μm in A; 25 μm in B and C.

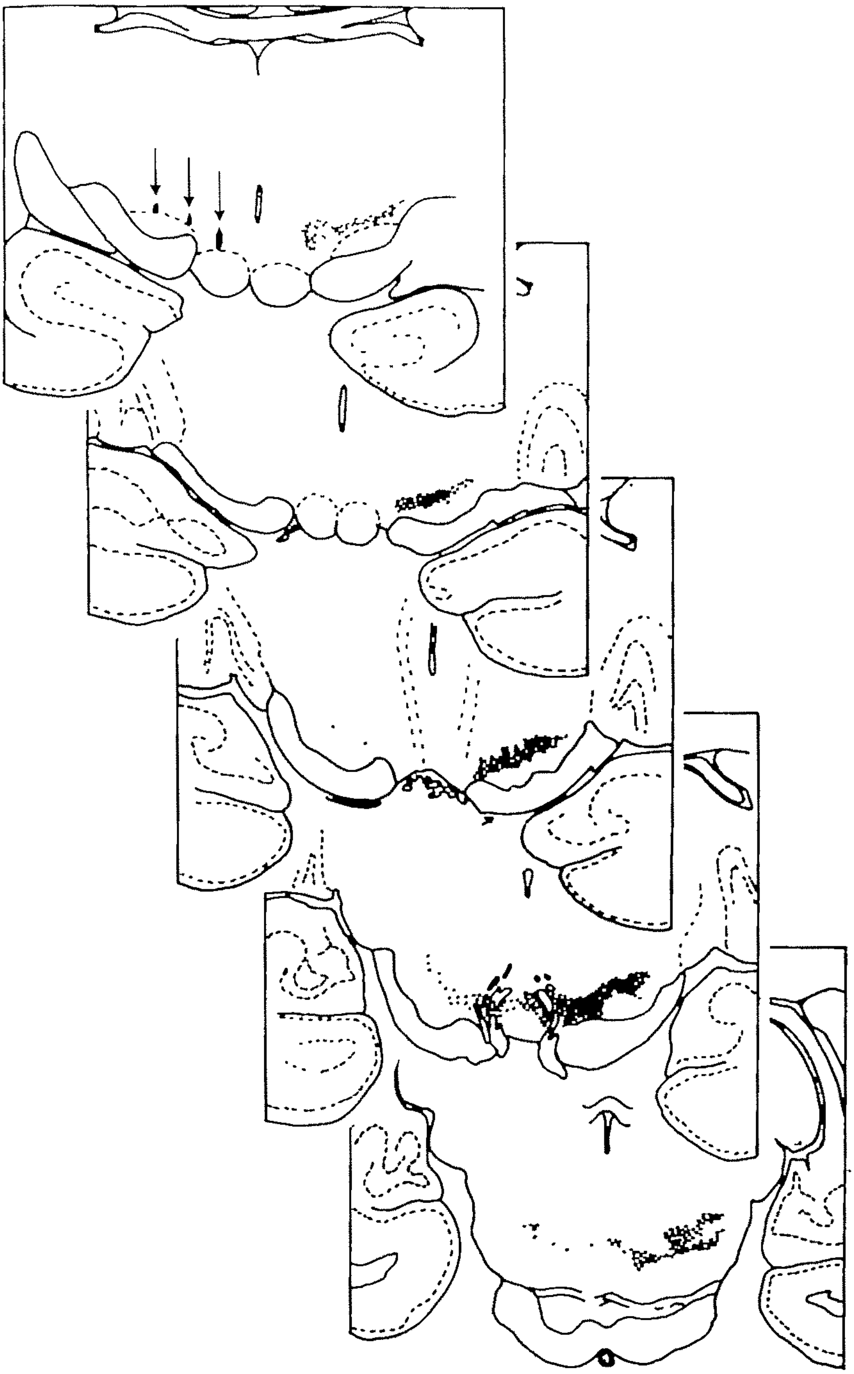

FIG. 2 Camera lucida drawings of THir cells remaining in the intact (*right*) and lesioned (*left*) substantia nigra of monkey L6 The regions of gliosis associated with the injections are indicated by the filled areas on the left of the first section.

the vicinity of the medial forebrain bundle. The extent of neuronal loss is illustrated (Fig. 2) in camera lucida drawings through the ventral mesencephalon of the case with the least extensive forebrain depletion (L6). Whereas cell loss was virtually complete on the lesion side in the more rostral parts of the substantia nigra in this case, some hundreds of THir neurons were seen to be spared in the most caudal parts of the substantia nigra and ventral tegmental area. The distribution of cells on the contralateral side was similar to that observed bilaterally in the four control cases. All other cases from the lesion group had more extensive cell depletions ipsilateral to the lesions, but complete sparing of the contralateral populations of THir cells.

A similar pattern of general cell loss in the pars compacta of the substantia nigra was seen in all stains. In the cresyl violet stained sections, the loss of large cells was associated with a moderate increase of small darkly stained glial cells. In the Masson-Fontana stain, neuromelanin pigment remained but was scattered diffusely through the pars compacta and was located extraneuronally. Whereas there was virtually complete loss of THir cells in the pars compacta, the few THir cells that survived the lesion appeared to exhibit an increased density of TH immunoreactivity (Fig. 1c), although we have not been able to quantify this observation.

In order to quantity the extent of cell loss induced by the lesions, cell counts were conducted through the substantia nigra. Sections were selected from each brain at the level of the third cranial (oculomotor) nerve and the total number of THir cells were counted in 250 μm wide bands moving laterally from either side of the midline. As shown in Fig. 3 the highest density of cells was found in the body of the substantia nigra pars compacta between 1 mm and 3 mm lateral from the midline, with a lower

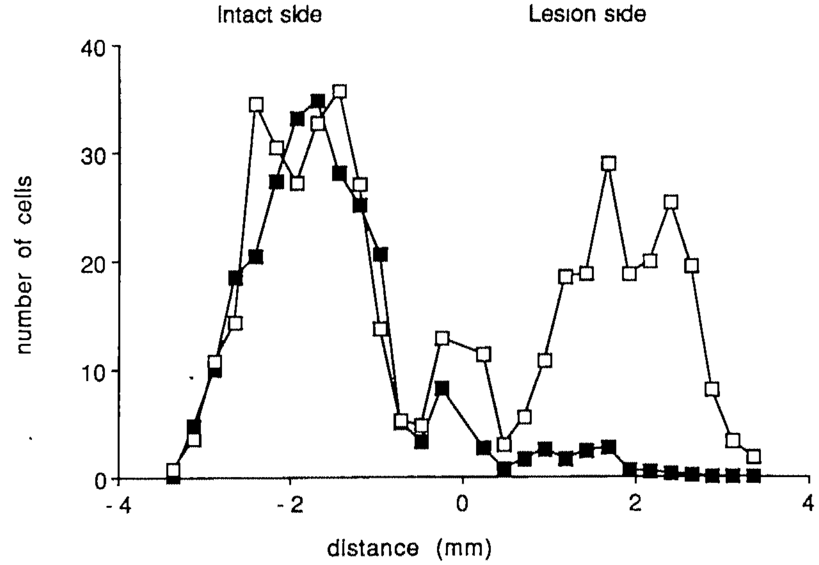

FIG. 3. Numbers of THir cells counted in the substantia nigra in sections selected from each brain at the level of the third cranial (oculomotor) nerve. Cells were counted in 250 μm bands moving laterally from either side of the midline, in the brains of the lesioned (closed squares) and sham operated control (open squares) animals.

density both in the more medial ventral tegmental area and in lateral parts of the substantia nigra. There was no difference between the six lesion and four control brains on the side contralateral to the lesion, whereas there was a 94% reduction in the number of surviving cells ipsilateral to the lesion. The greatest sparing was seen in the ventral tegmental area medial to the oculomotor cell roots, whereas cell loss was close to 100% in the central and lateral parts of the substantia nigra. ANOVA indicated a highly significant interaction between group and side [$F(1,8) = 48.2$, $P < 0.001$].

Biochemistry

The results of the biochemical assays of transmitter levels are shown in Table 1. Dopamine levels in the caudate and putamen were around 10 ng/mg of wet weight tissue on the intact side of the lesioned monkeys and on both sides of the control monkeys, in line with published reports of striatal DA content in this species (Sambrook *et al.*, 1979; Jenner *et al.*, 1984; Allen *et al.*, 1986). The DA content of the nucleus accumbens was somewhat lower at around 3 ng/mg. In the frontal cortical sites at which DA content was assessed (dorsolateral, medial and orbital), levels of the transmitter were much lower at around 0.04 ng/mg tissue.

The depletions of DA produced by the 6-OHDA lesion were substantial, falling within the range 93–100% at all of the striatal sites measured in all seven lesioned monkeys. Depletions in the frontal cortex were more variable, but mean DA depletions were still

TABLE 1 NEUROTRANSMITTER LEVELS AT STRIATAL, CORTICAL AND HYPOTHALAMIC SITES IN 6-OHDA LESIONED AND SHAM OPERATED MARMOSETS

	Lesion (n = 7)		*Sham (n = 6)*		*Percentage depletion*
ng/mg tissue	*Ipsi*	*Contra*	*Ipsi*	*Contra*	
Dopamine					
Caudate (a)	0.122±0.070	9.587±0.750	9.537±0.790	11.462±1.120	98.7***
Caudate (m)	0.124±0.083	9.666±0.804	10.814±1.197	14.097±1.019	98.7***
Caudate (p)	0.110±0.080	14.848±2.203	11.328±1.195	11.830±1.411	99.2***
Putamen (a)	0.155±0.129	9.754±1.308	10.722±1.281	12.518±1.306	98.4***
Putamen (p)	0.124±0.069	12.662±1.508	10.774±1.471	13.673±1.564	99.0***
N. accumbens	0.032±0.021	2.649±0.312	3.734±0.269	4.209±0.562	98.8**
FCX: dorsolat.	0.003±0.002	0.050±0.007	0.036±0.005	0.038±0.006	94.0***
FCX: medial	0.002±0.001	0.061±0.008	0.048±0.032	0.040±0.007	96.7***
FCX: orbital	0.004±0.002	0.047±0.008	0.032±0.005	0.045±0.008	91.5**
Noradrenaline					
Hypoth	0.263±0.022	1.163±0.099	1.382±0.119	1.538±0.197	77.4***
POA	0.154±0.027	0.979±0.197	1.334±0.237	1.681±0.315	84.3
Frontal CX	0.029±0.012	0.321±0.050	0.303±0.027	0.296±0.031	91.0***
Parietal CX	0.042±0.019	0.281±0.058	0.298±0.028	0.381±0.040	85.1*
Occipital CX	0.139±0.042	0.127±0.021	0.065±0.008	0.084±0.017	−9.4
Cerebellar CX	0.233±0.040	0.203±0.037	0.238±0.030	0.230±0.020	−14.8
5-HT					
Caudate (p)	0.148±0.044	0.528±0.047	0.288±0.024	0.273±0.048	72.0***
Putamen (p)	0.238±0.073	0.595±0.093	0.577±0.083	0.467±0.084	60.0**

a = anterior, m = mid, p = posterior, CX = cortex, FCX = frontal cortex, hypoth = hypothalamus, POA = preoptic area. Percentage depletion = (1 − lesion ipsi/lesion contra) × 100%. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ for ANOVA group × side interaction greater than 90%. ANOVAs revealed significant group (lesion vs sham) × side (ipsilateral vs contralateral) interactions for DA content at each of the nine sites at which DA levels were measured (*see* Table 1). In *post hoc t* tests differences between the ipsilateral and contralateral sides for the caudate, putamen and frontal cortex were significant at the $P < 0.001$ level, while for the nucleus accumbens the level of significance was $P < 0.01$. The sham injections had no significant effects on DA levels at eight of the nine sites, the one exception being mid-caudate [$t(5) = 4.59, P < 0.01$]. The DA content of the intact (i.e. contralateral) sides of the sham and lesioned monkeys did not differ, except in the mid-caudate [$t(11) = 3.71, P < 0.01$] and nucleus accumbens [$t(11) = 3.33, P < 0.01$] samples. These later differences appeared to have arisen from slightly above average levels in a couple of sham contralateral samples, rather than from especially low levels on the lesioned contralateral side.

Noradrenaline was also affected by the lesion. The depletions were significant in the hypothalamus, frontal and parietal cortices (*see* Table 1). In the preoptic area, the depletion just failed to reach a statistically significant level [$F(1,11) = 4.66, P = 0.054$]. Noradrenaline levels were unaffected in more posterior regions, i.e. in the occipital and cerebellar cortices.

5-Hydroxytryptamine, measured in the posterior caudate and putamen, was significantly reduced, although the depletions were not as substantial as those in the DA system (*see* Table 1).

Behavioural tests

Postion of the head. For the first few weeks following surgery, and in two cases (L5 and L8) for 2 mths, the lesioned marmosets tended to sit looking over their ipsilateral shoulder and rarely looked contralaterally [groups × side × months: $F(6,132) = 5.60, P < 0.001$; Fig. 4]. The time spent with the head ipsilateral relative to the rest of the body gradually declined [groups × post-lesion months: $F(5,55) = 2.53, P < 0.05$], but a significant ipsilateral bias was still present during the 6th post-operative month [$F(1,11) = 10.36, P < 0.01$].

While the overall ipsilateral bias remained, occasional switches to contralateral biases were also seen, particularly during the latter 3 mths of the experiment. Thus, all movements of the head by a lesioned animal might be towards the ipsilateral side during observations on one test day, but on the following test day only contralateral head movements would be seen. On the very next test day the ipsilateral bias usually returned. Whatever its direction the bias was usually complete, i.e. either 100% ipsilateral or 100% contralateral. The occasional episodes of contralateral biases (approximately 10% of observations) were only seen after about 60 d following surgery in five of the lesioned animals (L4, L5, L7, L9, L10) and were never seen in the other two. On any given test day it was not possible to predict the direction of bias except that the contralateral head movements tended to occur later in the day and when the monkeys were excited. The movements appeared to be qualitatively different from the ipsilateral bias which was very still and passive; typically the head drifted towards the contralateral side and was brought back to the midline with a jerk. During these episodes the monkeys had extreme difficulty in orienting towards the conveyer belt and were not normally tested on this or any other tasks at that time.

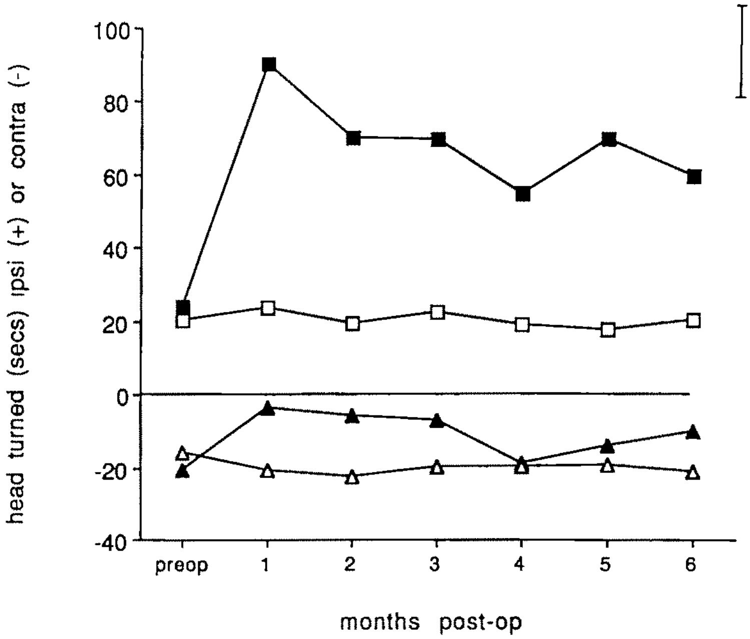

FIG. 4. Mean number of seconds head turned ipsilateral (squares) or contralateral (triangles) relative to the rest of the body of the lesioned (closed symbols) and control (open symbols) marmosets. The vertical bar indicates 2 SEM derived from the three-way interaction term of the ANOVA.

Rotation. Lesioned marmosets rotated, both spontaneously [F(1,11) = 6.43, $P < 0.05$; *see* Fig. 5A] and in response to an injection of amphetamine [square root transformation; F(1,11) = 5.09, $P < 0.05$; *see* Fig. 5B], predominantly towards the side of the lesion, i.e. ipsilaterally. Rotation rates varied considerably between animals. One lesioned marmoset (L8) rotated at around 5 turns/min spontaneously and 10 turns/min following amphetamine. Another lesioned marmoset (L6) did not rotate. The other five lesioned marmosets completed around 1–3 turns spontaneously and 1.5–5 turns/min under the influence of the drug. Rotation scores within animals across test sessions were generally consistent and did not decline over the 6 mths of testing. Consequently, since pre-operative data were not collected for these tests, the group×month interactions were not significant.

Occasional episodes of contralateral rotation were also observed during both the spontaneous and amphetamine rotation tests. A lesioned marmoset might rotate ipsilaterally initially, and then switch to contralateral rotation during the latter half of the test [spontaneous contralateral rotations, group×bin interactions: F(9,99) = 3.46, $P < 0.001$; *see* Fig. 6A]. Five of the lesioned marmosets (excluding L6 and L8) made these ipsilateral to contralateral switches. Switches in the other direction, from contralateral to ipsilateral, were never seen during tests.

Apomorphine induced contralateral rotation in all the lesioned marmosets except for L4 and L6 [F(1,11) = 5.41, $P < 0.05$]. Although there was a trend for the higher

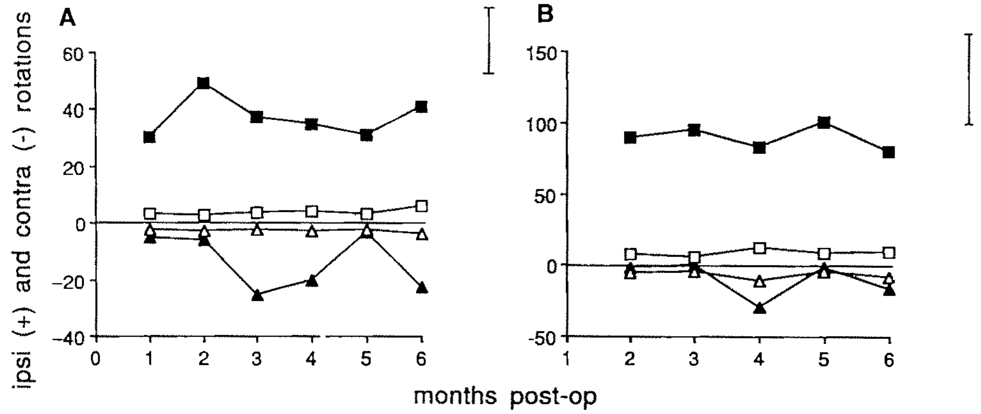

FIG. 5 A, mean number of spontaneous rotations. B, mean number of rotations following i.m. injections of amphetamine (0 5 mg/kg). Ipsilateral rotation (squares) is plotted above and contralateral rotation (triangles) below the x-axis for the lesioned (closed symbols) and control (open symbols) marmosets. The vertical bars indicate 2 SEM derived from the three-way interaction term of the ANOVAs.

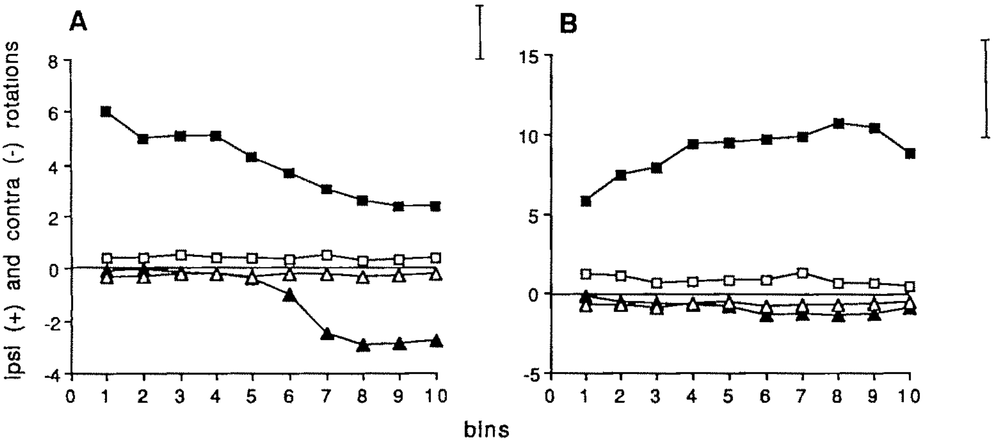

FIG. 6. Rotations in 10×3 min time bins (scores averaged across all post-operative rotation tests). A, spontaneous rotation. B, rotation following i.m. injections of amphetamine (0.5 mg/kg). Ipsilateral rotation (squares) is plotted above and contralateral rotation (triangles) below the x-axis for the lesioned (closed symbols) and control (open symbols) marmosets The vertical bars indicate 2 SEM derived from the three-way interaction term of the ANOVAs.

doses to induce more rotation, the group×dose interaction does not achieve statistical significance [F(3,33) = 2.35, $P < 0.057$; *see* Fig. 7]. At the highest dose most monkeys vomited and were slow to start rotating.

Activity. Spontaneous activity measured in the photocell cage was reduced by the lesion [square root transformation; F(1,11) = 4.06, $P < 0.05$; *see* Fig. 8A]. Neither apomorphine nor amphetamine consistently increased the activity of either the sham

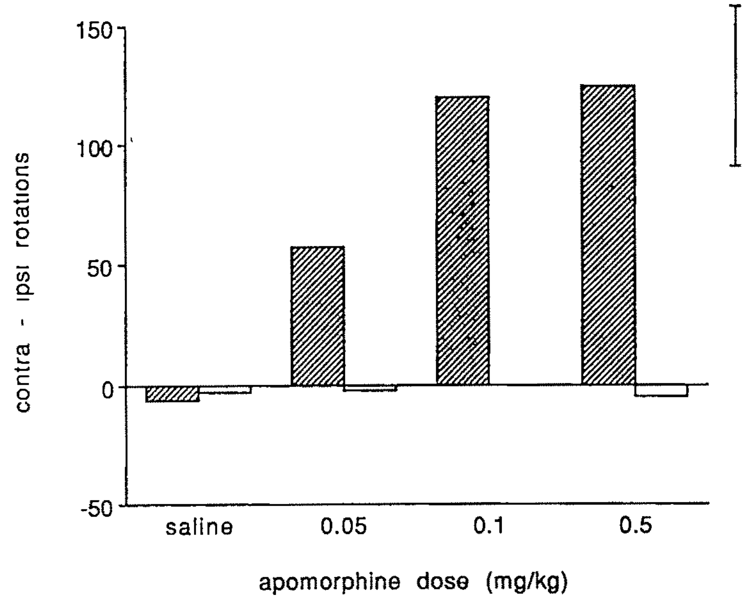

FIG. 7. Contralateral minus ipsilateral rotation following i.m. injections of ascorbate saline or apomorphine in the lesioned (hatched columns) and control (open columns) groups. The vertical bar indicates 2 SEM derived from the two-way interaction term of the ANOVA.

lesioned or the lesioned marmosets, thus no group×drug interactions were significant. The continued inactivity of the lesioned marmosets following injections of either saline or drug was apparent in both the apomorphine [square root transformation; F(1,11) = 13.31, $P < 0.01$; *see* Fig. 8c] and amphetamine tests (Fig. 8B), although in the latter case the effect of groups was not significant because of the high variability between scores.

Locomotor counts (different beam broken) as a percentage of total activity counts were low in the lesion group compared with the sham on all tests (e.g. for spontaneous activity: lesion 60.2% vs sham 71.6%). However, for both groups of animals, percentage locomotor counts tended to decrease as total activity levels declined. Thus, the low percentage locomotor scores of the lesion group were to be expected given their low total activity scores.

Conveyor belt: stationary apple. Before surgery only two of the 13 marmosets demonstrated a strong hand preference (>70% responses by one hand) when reaching for a stationary apple piece. One of these (L4) received lesion and the other (S15) sham injections on the side contralateral to the preferred hand. After surgery all seven lesioned monkeys demonstrated an almost complete ipsilateral response bias. This bias persisted at >85% in five monkeys for the 6 mths of tests. By the end of the first month L4 reverted to the strong contralateral bias shown pre-operatively, and L6 (DA depletion 93% putamen, 95% caudate, *see* Table 2) showed no clear hand preference. Figure 9A illustrates the significant post-operative ipsilateral bias in the lesion group compared with the sham [F(1,11) = 7.04, $P < 0.05$].

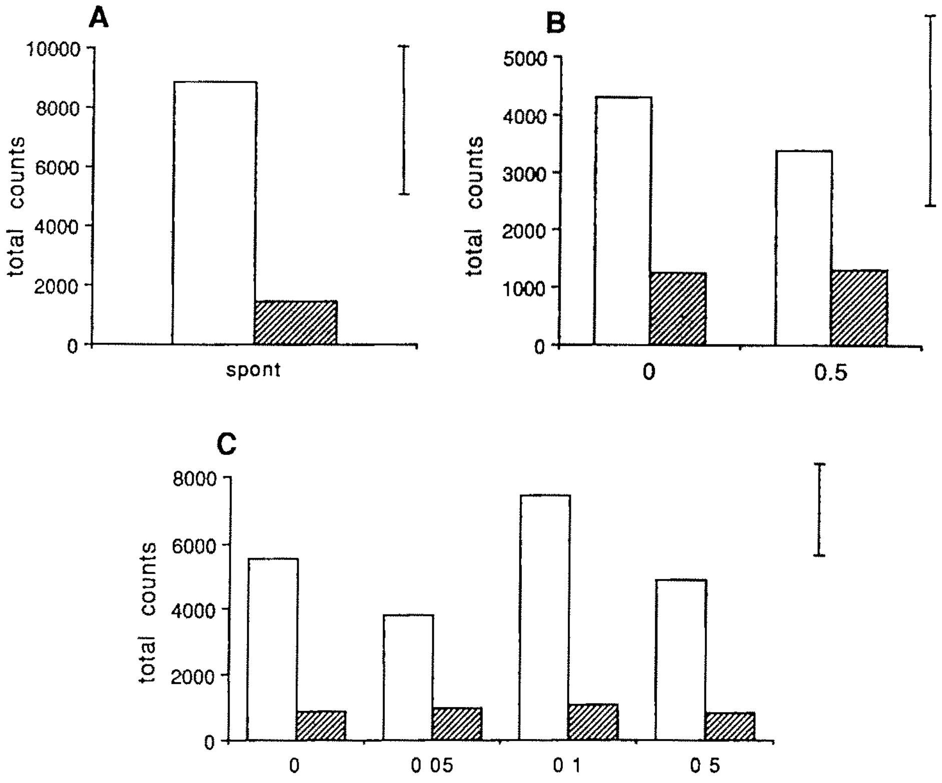

FIG. 8 Mean photocell counts in the activity cage. A, spontaneous activity. B, activity following i.m. injections of saline (0) and amphetamine (0.5 mg/kg). C, activity following i.m. injections of ascorbate saline (0) and three doses (0.05, 0.1 and 0.5 mg/kg) of apomorphine, in the lesioned (hatched columns) and control (open columns) groups. The vertical bars indicate 2 SEM derived from the one-way (A) or two-way (B and C) interaction term of the ANOVAs.

Conveyor belt: moving apple. Before surgery, most animals used the right hand to retrieve pieces of apple coming from the left, and the left hand for pieces coming from the right. L4 and S15 were the only monkeys with a pre-operative bias which overrode this tendency, preferring to use the same hand (which became the contralateral hand post-operatively) on all moving trials.

After surgery, the sham controls continued to reach with the contralateral hand for apple pieces arriving from the ipsilateral side, and vice versa (Fig. 9B). The lesioned monkeys showed a switch in hand preference to an ipsilateral bias, tending to use the ipsilateral hand even on those trials in which apple pieces arrived from the ipsilateral direction; the percentage of responses (including all attempts whether or not they were successful) made with the ipsilateral hand on the ipsilateral trials increased significantly in the lesion group compared with the sham [$F(6,132) = 3.53$, $P < 0.01$; *see* Fig. 9B]. This bias remained at >70% for 6 mths in five of the lesioned monkeys. L4 and L6 were exceptions in that they continued to use the contralateral hand on ipsilateral trials even during the first month after surgery.

On trials when the apple pieces arrived from the contralateral side the lesioned animals

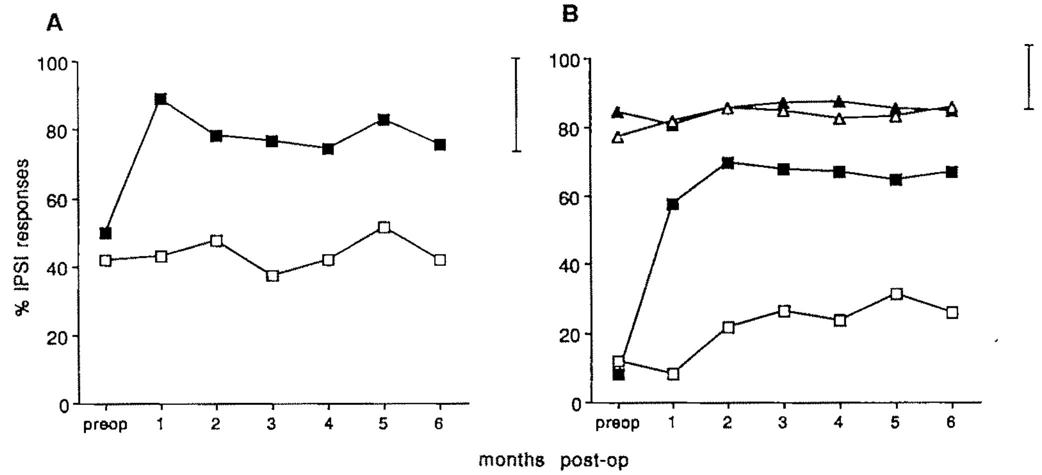

FIG. 9. Percentage of responses made with the ipsilateral hand in the conveyor belt tests by the lesioned (closed symbols) and control (open symbols) marmosets. A, responses for stationary pieces of apple B, responses (successful and unsuccessful) for moving apple pieces arriving from either the ipsilateral (squares) or the contralateral side (triangles). Vertical bars indicate 2 SEM derived from the two-way (A) or three-way (B) interaction term of the ANOVAs

showed marked neglect, failing to respond on many trials, although when they did respond the response was made as normal with the ipsilateral hand.The number of responses per 50 trials in which apple pieces came from each side is shown in Fig. 10. The group × side interaction was significant [F(1,11) = 14.78, $P < 0.01$], and *post hoc* tests showed that responses on contralateral [$t(11) = 5.19$, $P < 0.001$], but not ipsilateral [$t(11) = 1.63$, n.s.], trials were significantly reduced in the lesion group compared with the sham. Thus, the neglect was specific to the contralateral side. The deficit was striking to observe. The monkey might be sitting next to the belt looking straight ahead, apparently waiting for the next trial, but as the apple piece moved up from the contralateral side it would be ignored. Once the apple piece passed the midline the monkey would react and watch it go past, but it would be too late to make a response. If, on the next trial, the apple piece arrived from the ipsilateral side then it would be picked up and eaten with no apparent problem. L6 was the only lesioned monkey which did not neglect a contralateral apple piece immediately after surgery. All six lesioned monkeys which did show neglect recovered to some extent during the 6 post-operative months; the group × side × month interaction was significant [F(6,132) = 2.72, $P < 0.05$], and more responses were made by the lesioned monkeys on contralateral trials during the 6th mth than during the 1st mth [$t(6) = 4.45$, $P < 0.01$]. Despite this recovery, a significant impairment remained 6 mths after surgery [$t(11) = 2.96$, $P < 0.05$; *see* Fig. 10].

Conveyor belt: increasing speeds. The percentage of response attempts which ended in error, i.e. 'fails' and 'misses', rose in both groups as the speed of the belt increased (Fig. 11). By contrast, hand preference was not affected by the speed of the conveyor belt. Responses on trials in which apple pieces came from the ipsilateral side were more likely to result in error if the ipsilateral hand was used rather than the contralateral hand (Fig. 11A). Similarly, on trials in which apple pieces came from the contralateral side

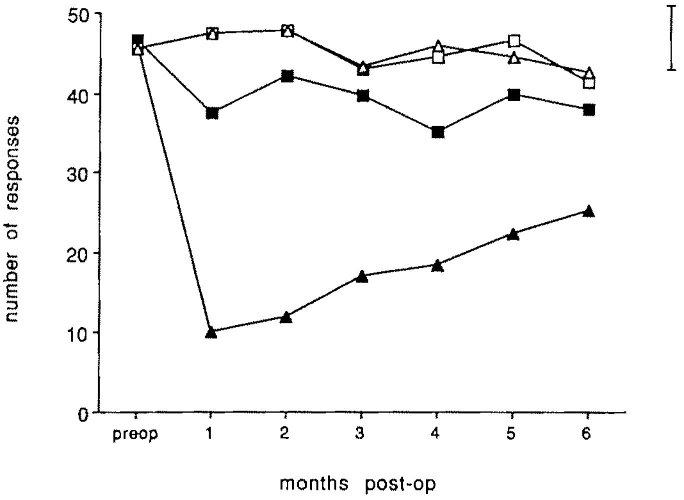

FIG 10. Number of moving conveyor belt trials on which a response was attempted (irrespective of hand used) by the lesioned (closed symbols) or control (open symbols) marmosets when apple pieces arrived from the ipsilateral (squares) or the contralateral (triangles) side The vertical bar indicates 2 SEM derived from the three-way interaction term of the ANOVA

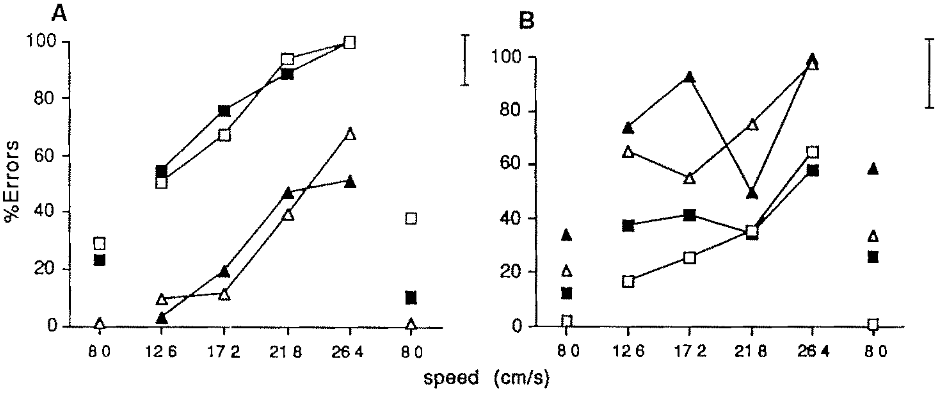

FIG 11. Percentage of response attempts which ended in error (i.e. 'fails' and 'misses', as defined in Methods) as the speed of the conveyer belt increased. Percentage errors with the ipsilateral hand (squares) and with the contralateral hand (triangles) by the lesioned (closed symbols) and control (open symbols) marmosets on trials when apple pieces arrived from the ipsilateral (A) or from the contralateral (B) sides. Vertical bars indicate 2 SEM derived from the three-way interaction term of the ANOVA.

errors were more likely on response attempts with the contralateral hand than with the ipsilateral hand (Fig. 11B). There was, however, no evidence that the lesion influenced the percentage of errors with either hand at any of the speeds [F(5,150) = 0.88, n.s.]. Thus, on moving conveyor belt trials, the main effects were on whether a response was attempted and which hand was used in an attempt (Figs 9, 10), and not on the accuracy of a response once under way.

Stationary apple pieces in a row. Confronted with six pieces of apple in a row on the stationary conveyor belt the monkeys with sham lesions tended to take the innermost pieces from both sides before removing those furthest from the centre. In contrast, the lesioned monkeys removed all three pieces from the ipsilateral side before taking the three on the contralateral side [group×side×position: F(2,44) = 9.87, $P < 0.001$; *see* Fig. 12A]. The contralateral apple pieces were not, however, completely ignored by the lesioned monkeys and were quickly removed after the ipsilateral apple pieces had been taken. The latencies to take apple pieces from the six positions were significantly affected by the lesion [group×side×position: F(2,44) = 5.84, $P < 0.01$], largely because the lesioned monkeys were fast compared with the controls at removing apple pieces from the ipsilateral side and not because they were particularly slow to take apple pieces from the contralateral side (Fig. 12B). Thus, the lesion affected the order in which ipsilateral and contralateral apple pieces were dealt with, but did not prevent animals from positioning themselves in the test cage so that they were able to take apple pieces from the contralateral side of the conveyer belt.

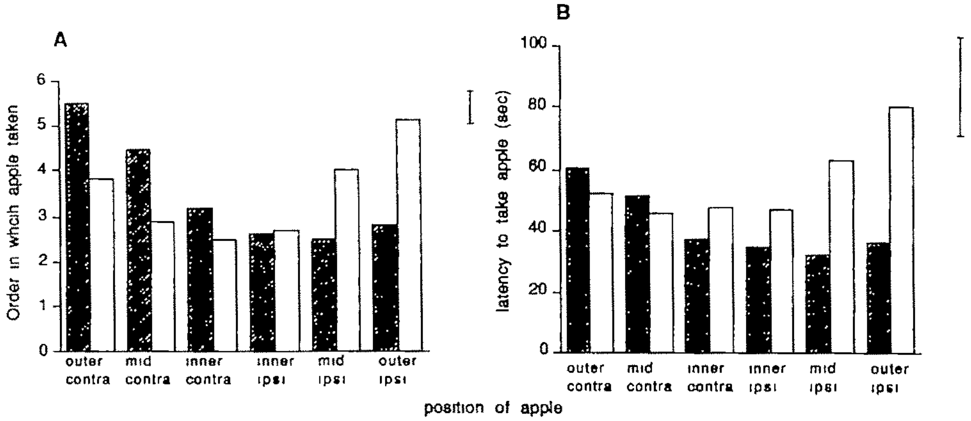

FIG. 12. Order (A) and latencies (B) to remove six pieces of apple placed in a row in front of the lesioned (hatched columns) and control (open columns) monkeys on the stationary conveyer belt The six positions were designated as the inner (closest to the midline), mid, or outer (furthest from the midline) positions ipsilateral and contralateral to the middle. On each trial, the serial order and latency to remove each piece was recorded, and averaged over 10 trials for each monkey Thus, low order scores indicate that apple pieces placed at these positions tended to be removed before apple pieces placed elsewhere. Vertical bars indicate 2 SEM derived from the three-way interaction term of the ANOVAs.

Adhesive labels. The lesioned marmosets contacted the label on the ipsilateral foot before that on the contralateral foot on more trials than the marmosets with sham lesions [F(1,11) = 13.10, $P < 0.01$; *see* Fig. 13A]. They also removed the ipsilateral label before the contralateral label more often than controls [F(1,11) = 10.95, $P < 0.01$;

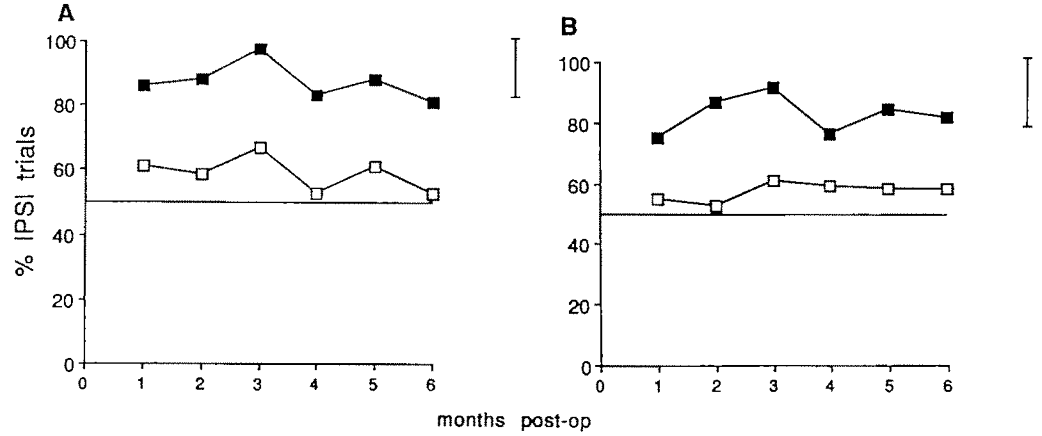

FIG. 13. Percentage of trials (six trials each month) on which the adhesive label around the ipsilateral foot was contacted (A) and removed (B) before that on the contralateral foot by the lesioned (closed symbols) and control (open symbols) marmosets. Vertical bars indicate 2 SEM derived from the two-way interaction term of the ANOVAs.

see Fig. 13B]. This ipsilateral bias was very stable across the 6 mths of tests and was apparent in six of the lesioned animals (all except L4). The lesioned marmosets were also slower than the sham to contact and remove both labels (Fig. 14A,B), and they were significantly slower to contact the contralateral label [group×side: F(1,11) = 8.49, $P < 0.05$]. When removing the labels they also tended to be slower to remove the contralateral than the ipsilateral label, although in this case the group×side interaction did not achieve statistical significance [F(1,11) = 4.38; $0.05 < P < 0.1$].

On trials when labels were placed unilaterally around only one foot, the lesioned

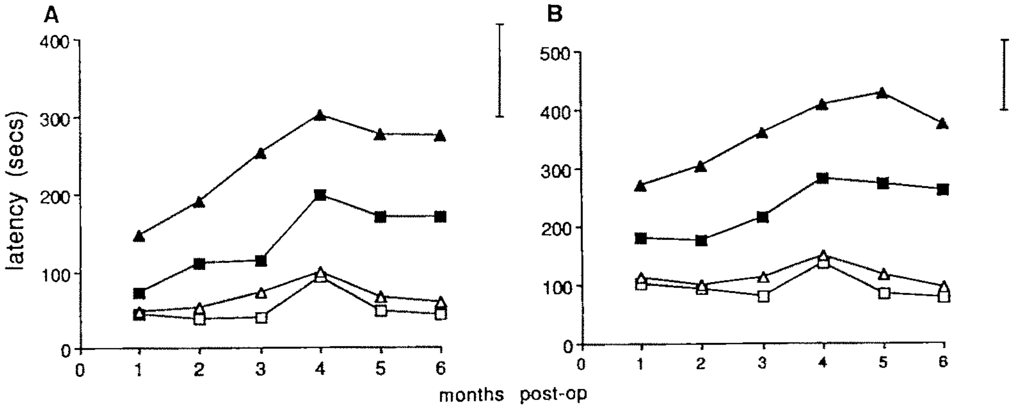

FIG. 14. Latencies to contact (A) and remove (B) adhesive labels placed bilaterally around the ipsilateral (squares) and the contralateral (triangles) feet by the lesioned (closed symbols) and control (open symbols) marmosets. Vertical bars indicate 2 SEM derived from the three-way interaction term of the ANOVAs.

marmosets were again slow to contact and to remove labels placed either ipsilaterally or contralaterally with relatively greater response times to contralateral labels (Fig. 15A,B). Although there were slight increases in the latencies to contact and to remove contralateral labels in the bilateral compared with the unilateral condition, these increases were not statistically significant. Thus, the impaired response to a contralateral label did not depend on the presence of a label in the ipsilateral foot.

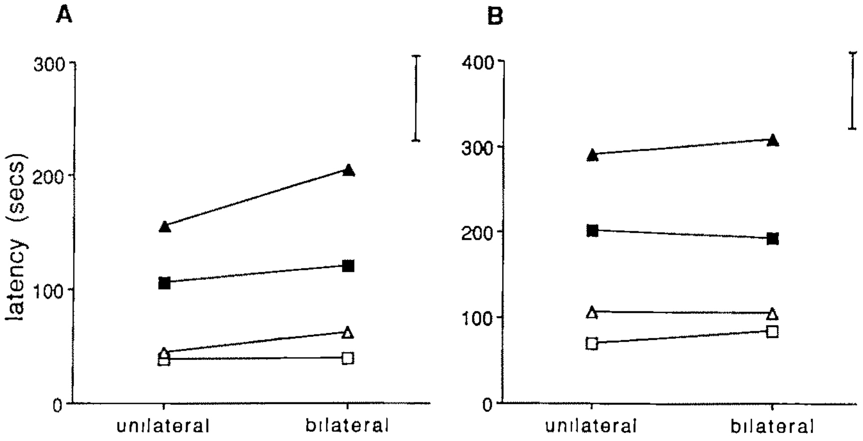

FIG. 15. Latencies to contact (A) and remove (B) adhesive labels placed either unilaterally or bilaterally around the ipsilateral (squares) and the contralateral (triangles) feet by the lesioned (closed symbols) and control (open symbols) marmosets. Vertical bars indicate 2 SEM derived from the three-way interaction term of the ANOVAs.

Reducing the size of the label on the ipsilateral compared with that on the contralateral foot did not influence the lesioned marmosets choice of the ipsilateral before the contralateral label or the latencies to respond to the two labels. Although there were reductions in the percentage ipsilateral contact bias (Fig. 16A) and the contralateral contact latency (Fig. 16C) when the ipsilateral label was one-half or one-quarter the size of the contralateral label, these changes were not statistically significant and there were no such trends in the removal data (Fig. 16B,D).

Comparisons between biochemistry, histology and behaviour

In order to compare performance on the different tests, summary scores for individual lesioned monkeys on each of the behavioural tests are presented together with biochemical and histological measures of the lesion in Table 2. The DA depletions in six of the lesioned monkeys were very similar and thus there was not enough between animal variability to permit statistical comparisons of correlations between DA levels and behaviour. One monkey (L6), however, had noticeably more DA remaining in the lesioned striatum than the other members of the group. Even though the depletions in this case were substantial (93% at one putamen site and 95% at most of the other striatal sites at which DA was measured), they were not as great as the >97% depletions measured in the six other lesioned monkeys. Behaviourally, the effects of L6's lesion were not as severe

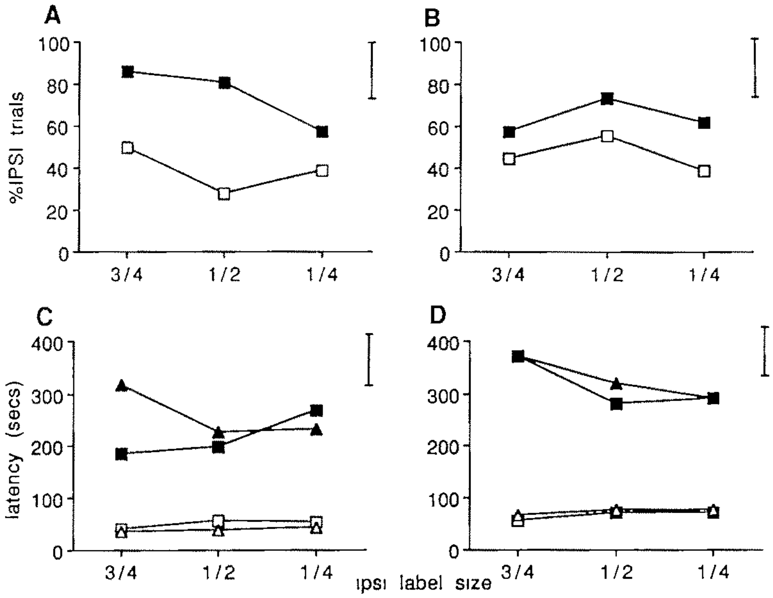

FIG. 16 Sensorimotor threshold test, with different sized labels on the ipsilateral foot, being either three-quarters, one-half or one-quarter the width of the label on the contralateral foot. The top panels indicate the percentage of trials on which the ipsilateral label was contacted (A) and removed (B) first by the lesioned (closed symbols) and control (open symbols) marmosets The bottom panels indicate the latencies to contact (C) and remove (D) ipsilateral (squares) and contralateral (triangles) labels. Vertical bars indicate 2 SEM derived from the two-way (A and B) and the three-way interaction term of the ANOVAs.

(Table 2). There was no clear correlation between the number of cells remaining in the lesioned nigra of L6 (at least at the level of the oculomotor nerve at which cell counts were made) and the biochemical or behavioural measures.

Spontaneous rotation and amphetamine-induced rotation by the lesioned monkeys correlated highly with each other (r = 0.950), and both these measures correlated with the time spent with the head ipsilateral with respect to the rest of the body (r = 0.770 and r = 0.867, respectively). Apomorphine-induced rotation did not correlate with spontaneous or amphetamine-induced rotation, but did correlate with time spent with the head ipsilateral (r = 0.723) and with hand preference (r = 0.782) and neglect at the conveyor belt (r = −0.798). Hand preference and neglect at the conveyor belt were also correlated with each other (r = −0.923) and with time spent with the head ipsilateral (r = 0.790 and r = −0.853, respectively). None of the other behavioural measures as presented in Table 2 were significantly correlated with each other, apart from the percentage of trials on which the label on the ipsilateral foot was contacted first and spontaneous activity (r = −0.836).

DISCUSSION

The present study has sought to characterize the behavioural impairments produced by unilateral DA depletion in the marmoset. A series of behavioural tests have been designed for the purpose of quantifying the severity and duration of the lesion effects

TABLE 2. COMPARISONS BETWEEN HISTOLOGY, BIOCHEMISTRY AND BEHAVIOUR FOR INDIVIDUAL 6-OHDA LESIONED AND SHAM OPERATED MARMOSETS

			Test												
			1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*
Monkey	*Sex*	*Side of injection*	*Cell count*	*Cd (a) DA*	*Put (a) DA*	*N Acc DA*	*Head ipsi*	*Spont rotation*	*Amphet. rotation*	*Apom rotation*	*Spont activity*	*Hand pref*	*Con Belt neglect*	*Percentage ipsi contact*	*Latency contra*
L4	F	L	–	0.13	0.09	0.10	52.2	2.26	1.59	0.07	43.3	16.8	25.5	63.8	172.2
L5	M	R	0	0.16	0.03	n.d	82.3	0.47	1.50	3.73	13.5	99.7	2.6	100.0	579.4
L6	M	L	19	0.56	0.93	0.12	25.9	0.19	0.18	0.03	5.6	1.3	47.4	88.9	107.0
L7	F	R	31	n.d	0.03	n.d.	56.1	0.87	0.79	6.91	12.6	74.3	9.3	97.2	175.3
L8	F	R	14	n.d	n.d	n.d.	116.7	5.81	10.64	7.89	23.1	92.9	1.8	80.5	52.4
L9	M	R	25	n.d	n.d	n.d	65.5	1.34	1.56	3.83	8.5	88.8	15.5	85.5	345.5
L10	M	L	3	n.d	n.d	n.d.	83.5	2.25	4.95	3.66	7.1	83.9	10.1	94.4	257.9
Lesion mean ± SEM			15.3	0.12	0.15	0.03	68.9	1.88	3.03	3.73	16.2	65.4	16.0	87.2	243.9
			±4.9	±0.07	±0.13	±0.02	±10.9	±0.72	±1.39	±1.14	±5.0	±14.9	±6.1	±4.7	±69.3
S11	F	R	115	9.60	8.39	3.22	18.1	0.13	0.23	0.14	297.7	36.2	49.0	80.5	41.7
S12	M	L	248	11.41	11.71	2.84	20.2	0.09	0.29	0.09	61.8	35.5	49.3	72.2	66.3
S13	F	L	–	11.10	13.88	4.43	20.6	0.17	0.21	0.21	34.4	9.9	45.4	38.8	26.4
S14	F	R	172	10.02	15.04	3.73	17.1	0.27	0.15	0.25	105.6	44.5	42.7	38.8	36.1
S15	F	L	–	8.99	6.35	3.67	28.8	0.23	0.15	0.11	27.6	3.1	41.9	55.5	74.4
S16	M	R	282	6.06	8.97	4.52	19.2	0.26	0.79	0.19	43.1	2.8	45.6	63.9	155.9
Sham mean ± SEM			204.0	9.54	10.72	3.73	20.7	0.19	0.30	0.17	95.0	22.0	45.6	58.3	66.8
			±37.6	±0.79	±1.28	±0.27	±1.6	±0.03	±0.10	±0.03	±42.1	±7.7	±1.3	±7.0	±19.3
Max score			–	–	–	–	180	–	–	–	–	100	50	100	600

Lesioned monkeys are L4–L10, sham injected monkeys are S11–S16. Scores for tests 5–7 and 10–13 are mean scores from all post-lesion tests. 1. Total number of THir cells in a section through the substantia nigra at the level of the third cranial (oculomotor) nerve. 2, 3 and 4. Striatal DA levels (ng/mg wet weight tissue) ipsilateral to the lesion or sham injection. a = anterior sample. n.d = not detectable. The minimum level of DA detectable by the HPLC was 0.025 ng, thus the DA content of n.d samples was taken to be 0.025 ng/weight of tissue sample for the purpose of calculating mean DA levels. 5. Number of seconds head turned ipsilateral relative to the rest of the body. Mean scores from all post-lesion tests (including those in which lesioned marmosets 'switched' direction from ipsilateral to contralateral). 6 and 7. Ipsilateral-contralateral rotations/minute, either spontaneous (6) or following an i.m. injection of 0.5 mg/kg amphetamine (7). Mean scores from all post-lesion tests (including those in which lesioned marmosets 'switched' direction from ipsilateral to contralateral). 8. Contralateral rotations/minute following i.m. injections of 0.05, 0.1 and 0.5 mg/kg apomorphine. 9. Spontaneous activity counts/minute. 10. Percentage responses with the ipsilateral hand on moving conveyor belt trials on which apple pieces arrived from the ipsilateral side. 11. Number of response attempts (irrespective of hand used) on trials on which apple pieces arrived from the contralateral side. 12. Percentage trials on which the adhesive label on the ipsilateral foot was contacted before that on the contralateral foot. 13. Latency (seconds) to contact the adhesive label on the contralateral foot.

over a period of months. It has been found that 6-OHDA lesions can reliably deplete the striatum of DA and that the battery of behavioural tests provides a powerful and efficient system for assessing the integrity of the nigrostriatal system in the marmoset.

The unilateral 6-OHDA injections made into the nigrostriatal bundle produced a substantial loss of THir cells from the substantia nigra and depletions of DA from the striatum and frontal cortex on the side of the lesion. Noradrenaline levels in the frontal cortex and hypothalamus, and 5-HT levels in the striatum, were also reduced. A major aim of the study was to produce dopaminergic lesions which were both substantial and reliable in terms of the extent of lesion damage inflicted across individual animals. The lesions were successful in this respect since in all the lesioned marmosets DA depletions exceeded 93% compared with control levels on the non-lesioned side. In six of the seven lesioned marmosets the depletions exceeded 97% at all of the six striatal sites at which DA was measured.

Persistent behavioural impairments lasting at least 6 mths were recorded on all of the tests in the lesioned marmosets as a group compared with sham lesioned controls, although individual marmosets sometimes recovered or showed no initial deficit on some tests. An important factor determining the likelihood of behavioural recovery was clearly the extent of lesion damage. The one lesioned marmoset which sustained DA depletions of only 93% in the putamen and 95% in the caudate nucleus and nucleus accumbens showed transient behavioural impairments which lasted no longer than 10 days. The only behaviours which may still have been affected in this animal 6 mths after surgery were sensorimotor neglect and spontaneous activity (*see* Table 2). In a pilot study, three marmosets (L1, L2, L3) which received 6-OHDA injections at only two or three sites in the nigrostriatal bundle, and sustained DA depletions in the striatum ranging from 60% to 80%, also showed behavioural impairments which lasted only a matter of days (unpublished data). These transient impairments were in striking contrast to the persistent impairments observed in the six marmosets which sustained DA depletions in excess of 97% of all striatal sites. Parkinsonian patients typically do not begin to manifest clinical symptoms of the disease until the DA content of the striatum is reduced to below about 80% of normal levels (Hornykiewicz, 1982), but at autopsy losses in the putamen may be 95% or more (Kish *et al.*, 1988). Correlations between lesion extent and symptom severity have been reported in rodents (Stricker and Zigmond, 1976) and monkeys (Kraemer *et al.*, 1981; Schultz *et al.*, 1989; Apicella *et al.*, 1990), with depletions in excess of 90% being essential for long-term behavioural effects. Mean striatal DA depletions of 96% were reported in rats which did not recover from the somatosensory deficits induced by a unilateral 6-OHDA lesion (Marshall, 1979). Two recent reports also suggest that about 95% may be the crucial level below which recovery does not occur. A group of vervet monkeys which were asymptomatic after MPTP treatment had putaminal DA depletions ranging from 75% to 99%, whereas in symptomatic monkeys DA losses were greater than 95% in all cases (Elsworth *et al.*, 1989). Extracellular concentrations of striatal DA in rats, measured by *in vivo* dialysis, were only modestly decreased by bilateral 6-OHDA lesions of 80–95%, but lesions which exceeded 95% produced a marked drop in extracellular concentrations (Castaneda *et al.*, 1990). Thus, the probability of spontaneous behavioural recovery may depend more on the extent of DA depletion than the type of toxin (6-OHDA or MPTP) used to produce the lesion. The advantage of the 6-OHDA lesion technique described here was the consistency with which depletions >95% were achieved ipsilateral to the lesions, with minimal damage to the contralateral side of the brain.

Despite apparently similar lesions biochemically and histologically, the six marmosets with the most extensive lesion damage were not equally impaired on all of the behavioural tests (*see* Table 2). In particular, rotation rates varied considerably between monkeys (although they were consistent within monkeys) and did not necessarily predict the severity of the lesion effects on other behavioural measures. For example, monkey L8 had the 'best' lesion with respect to rotation, but the 'worst' lesion with respect to the latency to contact the label on the contralateral foot. Subtle regional variations in striatal DA content and activity not revealed by the dissection used here may have been responsible for these differences. Elsworth *et al.* (1989) have emphasized dorsolateral vs ventromedial variations in DA content and homovanillic acid/DA ratios following MPTP treatment, with dorsolateral regions being more sensitive to the toxin. Alternatively, pre-operative performance on the behavioural tests may have influenced post-lesion recovery. For example, the one marmoset (L4) which recovered from the lesion-induced ipsilateral hand preference despite sustaining DA depletions in excess of 97%, did show a strong pre-operative bias for using the contralateral hand.

One of the purposes of using a range of measures was to look for an impairment which might be particularly sensitive to lesion damage and less prone to spontaneous recovery. Such a test might prove particularly useful in the assessment of potential therapies for Parkinson's disease, such as neural transplantation. The sensitivity and reliability of the different tests used here will be considered below in the discussion of the various lesion-induced behavioural impairments.

The most immediate and striking consequence of the lesion was the ipsilateral deviation of the head and the complete absence of head movements towards the side contralateral to the lesion. Crossman and Sambrook (1978) described marmosets with unilateral 6-OHDA lesions which exhibited torticollis such that the head was rotated by up to 180° in the caudal-cephalic axis and tilted upwards. In agreement with this and a subsequent report (Sambrook *et al.*, 1979), the severe deviation of the head observed in the present study gradually declined in most animals over a period of days to weeks. Although not always obvious to casual inspection, a pronounced ipsilateral bias in the position of the head was still evident on the formal tests 6 mths after surgery.

The spontaneous ipsilateral rotation observed on rotation tests and in the home cage appeared to develop from the head bias, indeed these two measures were significantly correlated. It seemed as if the lesioned marmosets were continually trying to look over their ipsilateral shoulder, thus any locomotion was necessarily in a circle. The ipsilateral rotation rate was increased by amphetamine, but only in those marmosets which rotated spontaneously. Similarly, the contralateral rotation induced by apomorphine was only seen in those marmosets which rotated spontaneously. Thus, drug-induced rotation was not a sensitive measure of DA loss since the marmoset with the least extensive depletion (L6, 93% putamen, 95% caudate) never rotated in response to either drug. Although in rats depletions of only 50% may be sufficient for amphetamine-induced rotation, not every rat with such a depletion, or indeed even a depletion as great as 95%, necessarily rotates (Hefti *et al.*, 1980). For those marmosets which did rotate, individual scores were generally stable and did not decline across months. Thus, rotation was a reliable measure in these animals, even though it was not a sensitive measure of DA loss in all animals.

Although the direction of bias remained predominantly ipsilateral throughout the experiment, periods of contralateral head bias and contralateral spontaneous and amphetamine-induced rotation were also observed in five of the seven lesioned marmosets. These temporary switches in the direction of bias may be equivalent to the 'paradoxical rotation' by rats with unilateral nigral lesions reported by Ungerstedt (1976). As in the rat study, this phenomenon was first seen about 2 wks after the lesion in animals with extensive depletions and its occurrence seemed to be related to stress, although Ungerstedt reported it as an immediate response to sudden stress, whereas in the present study it appeared to develop more gradually, e.g. during the second half of a rotation test (Fig. 6A). Stress-induced contralateral rotation has also been reported in monkeys with unilateral dopamine lesions (Bankiewicz *et al.*, 1986; Clarke *et al.*, 1989). The pharmacological/anatomical basis of the contralateral bias remains unclear, although it might involve activation of supersensitive receptors by transmitter released in response to the stressor. It did appear as if the contralateral side was 'switched on' during these episodes, whereas the more usual ipsilateral bias resulted from 'switching off' the contralateral side.

The lesioned marmosets were less active than controls on the spontaneous activity test and on all drug and vehicle tests in the photocell cage, even though the lesion was unilateral rather than bilateral. The absence of an increase in activity following the administration of amphetamine is consistent with previous reports that the drug does not increase locomotion in this species (Scraggs and Ridley, 1978; Ridley *et al.*, 1980). The failure of apomorphine to increase activity is more surprising since apomorphine has been reported to stimulate locomotion in intact marmosets (Ridley *et al.*, 1980) and DA receptor agonists induce locomotion in MPTP treated marmosets (Nomoto *et al.*, 1985; Temlett *et al.*, 1988). The doses of apomorphine used in the present study were behaviourally effective since they induced rotation. Perhaps the lesioned marmosets did not interrupt many photocell beams because they were rotating, hence the absence of an increase in activity. The lack of consistent stimulatory drug effects, together with the high variability between scores, limits the usefulness of activity as measured here for the purposes of the present model.

Shifts in paw preference towards an ipsilateral bias in rats following unilateral 6-OHDA lesions of the nigrostriatal dopaminergic pathway have been described in a number of studies (Siegfried and Bureš, 1980; Uguru-Okorie and Arbuthnott, 1981; Evenden and Robbins, 1984; Hamilton *et al.*, 1985; Whishaw *et al.*, 1986). In most of these reports the shifts were both long-lasting and profound compared, for example, with preference shifts produced by local anaesthesia of a limb or retraining (Hamilton *et al.*, 1985), or by small lesions of sensorimotor cortex or ibotenic acid lesions of the caudate-putamen (Whishaw *et al.*, 1986). In the present study, the ipsilateral hand preference in the lesioned marmosets as a group persisted for the 6 mths of tests. The severe nature of the shift was illustrated by the finding that the ipsilateral hand was preferred not only on simple tests of reaching for stationary apple pieces but also on trials in which the marmosets were required to reach for moving apple pieces arriving from the ipsilateral direction. The normal tendency on these trials pre-operatively and in the sham lesioned controls was to use the opposite (i.e. contralateral) hand. By choosing to use the ipsilateral hand the lesioned marmosets placed themselves in an awkward position for the reach and consequently made more errors. Like rotation, hand preference was a stable and reliable measure in those marmosets which exhibited an ipsilateral bias, but it was not a sensitive measure of DA loss *per se*, since hand preference was unchanged in the marmoset with the least extensive depletion. Also, an ipsilateral hand preference was not an inevitable consequence of even a substantial dopaminergic lesion as one other lesioned marmoset (L4), in this case with depletions >95% and long-term behavioural deficits on other measures, failed to show a persistent shift of preference. As suggested above, this may have been because of a strong pre-operative bias to use the hand contralateral to the lesion. Thus, factors other than asymmetries in DA innervation alone may influence hand preference.

The accuracy of reaching decreased as the speed of the conveyor belt increased. The finding that this measure was not affected by the lesion may seem surprising in view of reports of skill deficits and increased reaction/movement times in rats and monkeys with dopaminergic lesions (Sabol *et al.*, 1985; Whishaw *et al.*, 1986; Wolters *et al.*, 1988; Schultz *et al.*, 1989; Apicella *et al.*, 1990). However, it is important to note that the monkeys in the present experiment were given a free choice of which hand to use. Although some responses were made with the contralateral hand, these were very few in number and the main contributors of the contralateral responses shown in Fig. 11 were the two lesioned marmosets which did choose to use the contralateral hand. The other lesioned marmosets may well have shown skill deficits if they had been forced to use the contralateral hand (*cf* Whishaw *et al.*, 1986). Thus, the conveyor belt was useful for measuring hand preference and the number of response attempts, but not for assessing lesion effects on response accuracy with the contralateral hand.

Neglect has long been recognized as an important symptom of DA loss in experimental animals (Marshall and Teitelbaum, 1974; Ljungberg and Ungerstedt, 1976). The present study quantified two aspects of the neglect exhibited by the marmosets with unilateral 6-OHDA lesions: (i) a ipsilateral bias and increased latencies to contact and remove adhesive labels stuck around the feet; (ii) a decrease in the number of trials on which a response was attempted when apple pieces arrived from the contralateral side on the conveyer belt. Both measures revealed severe and long-lasting effects of the lesion. While neglect at the conveyor belt recovered somewhat during the course of the experiment, neglect of the adhesive label placed on the contralateral foot was a particularly robust effect of the lesion which did not recover. Even the marmoset with the least extensive DA depletion exhibited a reliable ipsilateral bias on this test. The sensitivity of the adhesive label test has been demonstrated in rats with unilateral 6-OHDA lesions by Schallert *et al.* (1983), who reported that apomorphine reversed the direction of bias at doses lower than those which induced rotation.

An important feature of the adhesive label test is that it measures neglect independently of postural and rotational asymmetries (Schallert *et al.*, 1982, 1983). This independence was evident in the present study: there were no correlations between adhesive label neglect and either the position of head bias or drug-induced rotation; the marmoset which never rotated (L6) did show neglect of the label on the contralateral foot, while the marmoset with the highest rotation scores (L8) was remarkably quick to contact and remove the contralateral label. The existence of such a dissociation is not surprising given evidence from rat studies that rotation and neglect of tactile stimuli may have different anatomical substrates within the striatum (Dunnett *et al.*, 1981; Dunnett and Iversen, 1982; Fairley and Marshall, 1986). The striatal circuits crucial for successful use of the hand may also differ from those involved in rotation (Sabol *et al.*, 1985;

Whishaw *et al.*, 1986; Pisa, 1988). Thus, subtle differences in the topography of the DA depletion between monkeys, although not detected in the results of the biochemistry, may have been responsible for the dissociation between rotation and neglect of the adhesive labels seen in the present study.

One disadvantage of the adhesive label test is that a bias can only be detected if the monkey responds to at least one of the two labels; in cases of very severe neglect and/or akinesia both labels may be ignored. Also, if the experimenter or test situation is unfamiliar, even control monkeys with no lesions may ignore the labels (personal observations). Thus, increased latencies alone are not a reliable measure of neglect. However, provided such factors are taken into account, the test would appear to be useful as a sensitive and yet simple measure of neglect in the marmoset.

The neglect at the conveyor belt was of a visual stimulus, i.e. the approaching apple piece, but the deficit was not necessarily a consequence of impaired input of visual sensory information. Similarly, impaired input of tactile sensory information may not have been the cause of neglect of the adhesive labels. Both tasks required motor responses to sensory events. It was argued above that neglect of the contralateral label was unlikely to have been an indirect consequence of the postural and rotational motor asymmetries produced by the lesion. However, the task does require direct contralateral movements of the head and hindlimb to bring the label on the contralateral foot to the mouth. At the conveyor belt contralateral movements of the head and body are required to prepare a response to apple pieces arriving from the contralateral side, even though the reach itself may be made with the ipsilateral hand. It was the absence of these anticipatory contralateral movements that appeared to be crucial in the failure of the lesioned marmosets to respond on the contralateral trials. Interestingly, given time, the lesioned marmosets were capable of positioning themselves so as to take apple pieces from the contralateral side when they were placed in a row on the stationary conveyor belt. However, on the moving conveyor belt trials, when the side from which the apple pieces might arrive was uncertain, all anticipatory movements were directed towards the possible arrival of apple pieces from the ipsilateral side. Thus, on both the adhesive label and conveyor belt tasks, neglect could have arisen because of problems initiating movements contralateral to the lesion. Tasks designed to tease apart sensory and motor deficits in neglect by requiring a motor response away from the sensory event suggest that the neglect produced by 6-OHDA lesions in rats (Carli *et al.*, 1985) and electrolytic lesions of the mesencephalic recticular formation in monkeys (Watson *et al.*, 1974) is primarily motor rather than sensory in origin. Thus, the neglect observed in the present study may well have resulted from a hemiakinesia rather than a sensory or hemi-inattentional disorder (Milner, 1987).

In summary, all of the behavioural tests used here revealed long-term effects of DA depletion in the lesioned marmosets as a group, although even with substantial depletions individual animals sometimes recovered on some tests. Thus, data from a group of lesioned monkeys rather than one or two individuals would appear to be essential as an adequate control for spontaneous recovery, however good lesions might be in biochemical or histological terms. Of the various behavioural tests used here, neglect of the contralateral adhesive label was perhaps the most sensitive to DA loss. The stability of rotation scores over the 6 mths of tests suggests that rotation may also be a useful behavioural measure in marmosets for assessing potential therapies for Parkinson's disease. The dissociation between neglect and rotation, however, cautions against the exclusive use of one test rather than the other, or indeed any attempt to predict recovery generally from improvements on a single behavioural measure.

The present study has been conducted as the first stage of developing a model of Parkinson's disease for assessing the functional efficacy of dopaminergic grafts in primates. A number of previous studies have approached this problem using the toxin MPTP, which is particularly suitable for making bilateral lesions. However, when such lesions are relatively complete the animals are profoundly debilitated and require considerable nursing care or L-dopa treatment (e.g. Clarke *et al.*, 1987), whereas when the lesions are incomplete the induced syndrome can show substantial or complete recovery over periods of a few days or weeks. By contrast, evaluation of neural grafts requires a long-lasting, stable set of impairments that is easily quantifiable in animals that are otherwise healthy. We have therefore chosen to pursue the alternative strategy of making unilateral lesions, with the intention of producing lateralized impairments. In this case the other side of the brain remains intact, and sustains the animal in full health. Monkeys with unilateral lesions can be trained or tested on tasks which severely affected bilaterally lesioned monkeys are unable or unmotivated to perform. In addition, side preferences can be quantified and performance with the unaffected (ipsilateral) side can be used as a control for that of the affected (contralateral) side. By contrast, behavioural testing of monkeys with bilateral lesions has been mostly limited to activity scores or observation rating scales, although recent reports have described cognitive and complex motor deficits in MPTP (bilaterally) treated monkeys (Schneider and Kovelowski, 1990; Taylor *et al.*, 1990*a*,*b*). Either intracarotid (Bankiewicz *et al.*, 1986) or central injections of MPTP (Imai *et al.*, 1988) or central injection of 6-OHDA can be effective for producing unilateral lesions. We have chosen the latter toxin since it is much safer to handle in the laboratory environment, and the primary benefit of MPTP (the ease of peripheral administration) is lost once the decision of making unilateral lesions sets the requirement for surgical (in this case stereotaxic) administration.

It should be noted that the unilateral 6-OHDA lesion model does not accurately reflect clinical Parkinson's disease in either symptomatology or neuropathology, although neglect (Villardita *et al.*, 1983; Starkstein *et al.*, 1987) and spontaneous rotation towards the hemisphere containing less striatal dopaminergic activity (Bracha *et al.*, 1987) have been reported in hemi-parkinsonian patients. Indeed, no present animal model reproduces the gradual onset, the slow decline and the great complexity of the human disease. However, accurate reproduction of the symptomatology is not the primary purpose of the model. Rather, the goal is to develop (i) surgical techniques to induce stable dopaminergic denervation and (ii) quantitative tests to characterize the resulting functional deficits, that enable novel therapeutic strategies for dopaminergic replacement to be assessed in primates over prolonged periods of time. Taken together, the tests and results described here provide such a model.

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MOTOR SEQUENCING WITH LEFT HEMISPHERE DAMAGE

ARE SOME COGNITIVE DEFICITS SPECIFIC TO LIMB APRAXIA?

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SUMMARY

Sixteen left-hemisphere stroke patients, who were apraxic or nonapraxic, and 17 control subjects performed sequences of hand postures that varied in the number of different postures (repetitive and heterogeneous) and sequence length (one to five). Performance of the left hand (ipsilateral to stroke) was compared with a control group using the left hand.

All stroke patients had slower reaction times and were slower to execute single hand postures, but the apraxic group was not slower than the nonapraxic group. Both the apraxic and the nonapraxic groups had similar problems scheduling or timing motor programs for both sequence types such that inter-response times were more affected by sequence length than the control group. However, only the apraxic group showed abnormalities in preprogramming heterogeneous sequences. The apraxic group also made more errors and had longer movement times (MTs) than for the other groups, but only for heterogeneous sequences containing more than three hand postures. The nonapraxic group did not show slower MTs or greater errors, regardless of the type or the length of sequences. These results suggested deficits in encoding, generating single movements and in scheduling or timing a series of actions which generally attributable to left hemisphere damage. However, abnormalities in temporal organization processes prior to and during movement were specific to apraxia. The dissociation between the two stroke groups on some but not all aspects of sequencing has implications for different cognitive mechanisms supporting motor sequencing.

INTRODUCTION

Left hemisphere damage is frequently accompanied by ideomotor limb apraxia, a disorder of skilled movement that cannot be attributed to weakness, sensory loss, language comprehension deficits or general intellectual deterioration. Clinical assessment of limb apraxia is based on an examination of gesture performance to command and/or imitation (e.g. brush teeth, salute, put finger on ear). Although apraxia and aphasia frequently coexist, apraxia is considered a cognitive-motor disorder because the degree of gestural disruption can be dissociated from aphasia severity or type (Goodglass and Kaplan, 1972; Lehmkuhl *et al.*, 1983; Rothi and Heilman, 1984), and severe apraxia has been reported in patients without language disturbances (Heilman *et al.*, 1973). Gestural disturbances in apraxia have been attributed to a variety of problems including difficulties integrating memory representations of intra- and extrapersonal space (Haaland and Flaherty, 1984), a loss or disruption in spatiotemporal memory codes (Heilman *et al.*, 1982; Rothi *et al.*, 1988; Poizner *et al.*, 1990) and encoding deficits (Faglioni *et al.*, 1990).

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The cognitive mechanisms of this disorder have been disputed, in part, because most investigations of gesture performance are based on clinical descriptions which rely heavily upon the performance of familiar movements and error analyses. Other characteristics of movement which may be disrupted are ignored. In particular, clinical descriptions of ideomotor apraxia do not specifically point to a sequencing deficit, yet many individual gestures require sequencing of several component movements.

Abnormalities in sequencing with left hemisphere damage have been examined most thoroughly in studies of largely unfamiliar movements, which when combined into sequences do not represent meaningful gestures. While many studies have reported greater sequencing deficits with left than right hemisphere damage (Kimura and Archibald, 1974; Kimura, 1982), others have shown that left hemisphere damage produces deficits in the performance of isolated movements (Kolb and Milner, 1981; Kimura, 1982; De Renzi *et al.*, 1983; Harrington and Haaland, 1991*a*). This latter finding suggests the possibility that sequencing deficits may be due to the cumulative effects of deficits in programming single movements, but when this problem was controlled, impaired sequencing was still evident (Harrington and Haaland, 1991*a*). Others have suggested that memory factors can explain left hemisphere specialization for sequencing (Roy, 1981; Jason, 1986; Roy and Square-Storer, 1990) whereas sequencing deficits with left but not right hemisphere damage even when memory was not required have also been reported (Harrington and Haaland, 1991*a*).

Few studies have directly examined whether cognitive deficits in limb sequencing with left hemisphere damage are specific to the disorder of apraxia or more general to the role of the left hemisphere in controlling a wide variety of movements (*see* Haaland and Harrington, 1990). The present study compared apraxic and nonapraxic patients with left hemisphere damage. Performance was examined on sequences of hand postures that varied in length and the number of different hand postures. Although most studies have been restricted to analyses of errors, the present study also examined reaction times (RTs) for correct movements to determine whether the cognitive operations utilized to carry out the action were completely normal.

Previously we reported that generating a motor plan prior to movement was intact with left hemisphere damage as sequence length had a similar effect on RTs of both patients and normal control subjects, regardless of sequence complexity (i.e. sequences containing repetitive vs different responses) (Harrington and Haaland, 1991*a*). However, if apraxia produces a deficit in identifying or recognizing the to-be-performed actions (Heilman *et al.*, 1982) or in the rate of retrieving subprograms for each response to assemble a motor plan (Harrington and Haaland, 1987), RTs should increase more with sequence length in the apraxic than the nonapraxic patients.

Programming difficulties during movement were examined by comparing apraxic and nonapraxic patients on inter-response times (IRTs) and movement times (MTs). The IRT analyses examined the effect of sequence length on the execution of a single posture within a sequence to determine whether programming during movement was influenced by the number of other responses within a sequence, not simply the individual hand posture. Inter-response times of patients with left hemisphere damage were more affected than those of control subjects by the number of other responses in a sequence, suggesting they engaged in more programming concerning the sequence while executing a single posture (Harrington and Haaland, 1991*a*). If this deficit is specific to apraxia, only the

IRTs of apraxic patients should vary with sequence length. At a different level of enquiry, the MT analyses summed across all IRTs within a sequence, and compared the difficulty of sequencing repetitions of a posture vs different postures (i.e. heterogeneous sequences) to examine programming processes related to sequencing movements with a more complex structure. Previously we found error rates and MTs for heterogeneous but not repetitive sequences increased as sequence length increased more in the left hemisphere-damaged patients, implicating deficits in some aspect of temporal organization. If these deficits are specific to the disorder of apraxia, only the apraxic patients will show this pattern of errors and MTs.

METHODS

Subjects

Seventeen normal controls and 16 left hemisphere-damaged stroke patients were tested at the Albuquerque Veterans Affairs and Lovelace Medical Centers. All subjects were right-handed males and performed the task with their left hand. The arm ipsilateral to the lesion was examined in the stroke group to avoid biasing the sample by excluding hemiplegic patients and to minimize factors that were purely motoric or sensory in nature.

All subjects were administered a 15-item apraxia battery (Haaland and Flaherty, 1984) consisting of five transitive (representational gestures with pretended object use), five intransitive (representational gestures without pretended object use) and five nonrepresentational gestures. Subjects were videotaped as they imitated unilateral limb movements and their performance was scored from the videotape. Errors were scored relative to the examiner's performance and consisted of six categories, described in detail by Haaland and Flaherty (1984): (i) perseveration; (ii) orientation; (iii) position of hand; (iv) body-part-as-object; (v) target; (vi) undue hesitations. Subjects who made any of these errors on five or more items were classified as apraxic. Table 1 shows seven of the patients who were classified as apraxic and nine of the patients who were nonapraxic. All of the control subjects scored within the normal range. There were no significant differences among the three groups in age or education level. Mann-Whitney U tests (Siegel, 1956) showed no significant differences between the apraxic and the nonapraxic groups in the mean number of months post-stroke (apraxic: mean = 40, SD = 42; nonapraxic: mean = 30, SD = 55). Two of the apraxic but none of the nonapraxic patients were classified as hemiplegic, with hemiplegia defined as contralateral grip strength more than two standard deviations below ipsilateral grip strength which was greater than zero.

All subjects were given the neuropsychological tests summarized in Table 1 to describe their visuospatial and language skills. Comparisons between groups used the Mann-Whitney U statistic. On the Block Design subtest of the Wechsler Adult Intelligence Scale-Revised Form (WAIS-R) (Wechsler, 1981), visuospatial organization skills in the apraxic group were significantly ($P < 0.025$) poorer than the nonapraxic group, the members of which were not impaired relative to those of the control group. Two of the apraxic patients and one nonapraxic patient scored below the lowest score of the control group on this test. Both the apraxic and the nonapraxic groups were similarly impaired relative to the control group ($P < 0.025$) on verbal fluency from the Cookie Theft picture of the Boston Diagnostic Examination of Aphasia (BDEA) (Goodglass and Kaplan, 1972). Comparisons between the two stroke groups on auditory comprehension from Part V of the Token Test (De Renzi and Vignolo, 1962) showed performance was significantly ($P < 0.05$) worse for the apraxic than the nonapraxic group which was not impaired relative to the control group. Two of the apraxic patients had moderate (9 errors) and two had severe (21 errors) auditory comprehension deficits, whereas the remaining patients scored within normal limits. The latter two apraxic patients also were severely dysfluent. In contrast, only one nonapraxic patient had severe auditory comprehension deficits (18 errors), but was only mildly dysfluent (5.8). The remaining patients had normal auditory comprehension.

Apparatus

Subjects executed sequences of hand postures on the apparatus depicted in Fig. 1. The apparatus was interfaced with a computer, and contained a row of five vertical plates which required contact with the lateral side of the hand, a row of five recessed buttons which required contact with the index finger with

TABLE I. DEMOGRAPHIC AND NEUROPSYCHOLOGICAL PROFILE OF SUBJECTS

	Apraxic group (n = 7)			*Nonapraxic group (n = 9)*			*Control group (n = 17)*		
	Mean	*(SD)*	*Range*	*Mean*	*(SD)*	*Range*	*Mean*	*(SD)*	*Range*
Age	63	7.5	55–76	63	6.9	51–76	63	6.5	56–75
Education	12	3.4	8–16	12	1.9	8–15	13	0.8	12–14
Apraxia severity[1]	7.4	2.4	4–10	13.3	1.4	11–15	13.6	1.3	11–15
Visuospatial organization[2]	6.0	1.4	4–8	9.1	2.5	5–14	10.7	2.8	6–14
Auditory comprehension[3]	10.4	7.8	0–21	4.1	5.5	0–18	1.8	2.0	0–7
Verbal fluency[4]	5.1	2.3	1.0–6.5	6.3	0.5	5.3–6.8	6.8	0.2	6.3–7.0

[1] Number of items correct out of 15 (Haaland and Flaherty, 1984).

[2] Scale scores from the Block Design subtest of the WAIS-R (Wechsler, 1981)

[3] Number of errors on Part V of the Token Test (De Renzi and Vignolo, 1962)

[4] Fluency rating based on the description of the Cookie Theft picture from the BDEA (Goodglass and Kaplan, 1972) Scores range from 0 to 7.

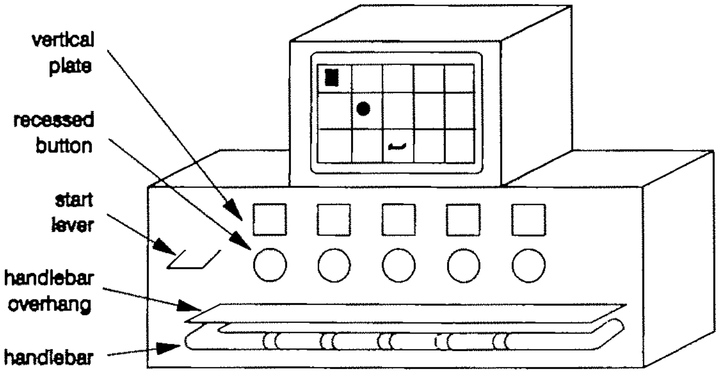

FIG. 1. Diagram of the hand-posture sequencing apparatus. The monitor situated above the apparatus depicts an example of a sequence.

the forearm pronated, and a row of five handlebars which required the four fingers to wrap around the bar from underneath with the forearm supinated. Subjects wore gloves equipped with metal contacts. The start plate was located to the left of the manipulanda, and subjects always moved from the left to the right. When a change in hand posture was made, subjects moved to the right diagonally (up or down) to the next manipulandum. A monitor presented pictorial displays of the entire motor sequence (*see* Fig. 1).

Procedure

Subjects began each trial by resting their index finger on the start plate which caused a pictorial display of the sequence to appear on the monitor. After a random delay ranging from 1 s to 2 s, a tone signalled subjects to begin the sequence. Upon completion of the last response in the sequence, the visual display terminated. Reaction time was measured from the onset of the tone to when subjects lifted their finger from the start plate. The first IRT was measured from when subjects left the start plate (i.e. the end of the RT interval) to the completion of the first response (i.e. contact with the manipulandum), and subsequent IRTs were measured from the completion of one response to the completion of the next. Movement time was measured from the end of RT to the completion of the last response in the sequence. An error trial was recorded when subjects took longer than 2000 ms to initiate the movement during the RT interval (i.e. error before movement) or to execute a single hand posture (i.e. error during movement), or if they executed the wrong hand posture (i.e. error during movement).

Design

Two types of sequences, repetitive and heterogeneous, were presented. Repetitive sequences varied in length from one to five responses with each length consisting of repetitions of plate (P), button (B), or handlebar (H) responses (i.e. P, PP, PPP, PPPP, PPPPP, B, BB, BBB, BBBB, BBBBB, H, HH, HHH, HHHH, HHHHH). Heterogeneous sequences varied in length from two to five responses and were constructed so that the first two responses were the same for all sequence lengths with the remaining response(s) consisting of the addition of the first response (i.e. PB, PBP, PBPP, PBPPP, HB, HBH, HBHH, HBHHH). Sequence type was blocked and block order was randomized across subjects. Each of the 23 different motor sequences was presented eight times across blocks in a random order. If subjects made an error, the trial was repeated randomly at the end of the block of trials. Subjects were required to correctly complete two practice trials of each of the 23 sequences.

Computerized tomography scan quantification

Computerized tomography scans were available on all stroke patients. Computerized procedures were used to quantify lesion size and location (anterior vs posterior) (Harrington and Haaland, 1991*a*). Lesion size was expressed as a ratio of lesion volume to brain volume. Lesion location was expressed as both volumetric and linear measures. The volumetric measures were the proportion of the total lesion volume that was located anterior and posterior to a line halfway between the frontal and occipital poles. The linear measures were the distance of the lesion from frontal and occipital poles divided by total distance so as to represent a proportion of the slice length. Computations of anterior and posterior distance were weighted by the lesion volume of each slice.

RESULTS

The analyses focused on the comparisons of the apraxic group with the nonapraxic and control groups. All RT and IRT analyses were based on a mixed model design with group (i.e. control, apraxic and nonapraxic) as the between-subject factor and sequence length as the repeated factor. Planned comparisons contrasted the performance of the apraxic, the nonapraxic and the control groups. Separate analyses of variance (ANOVAs) were conducted for each measure. Repetitive and heterogeneous sequences were analysed separately.

Movement times and errors during movement were analysed using a mixed model design with group as the between-subject factor and sequence length (two to five hand postures) and sequence type (i.e. repetitive vs heterogeneous) as the repeated factors. Because errors before movement were low and averaged 5% for all three groups, regardless of the length or the type of sequence, these data will not be discussed further. The sample of apraxic and nonapraxic patients was small. Thus, statistical tests exceeding the 0.05 experiment-wise α level were reported when there were clear trends for group differences (i.e. $P = 0.10$).

Cognitive processing prior to movement: reaction times

Repetitive sequences. To examine the apraxic and the nonapraxic patients' ability to preprogram repetitive sequences, the effect of sequence length on RT was analysed. In earlier studies (Harrington and Haaland, 1987, 1991*a*,*b*) it was shown that sequence length has little or no effect on RTs for repetitive movements, perhaps, because subjects impose an organization on the sequence such that they plan it as a single unit, regardless of the number of responses. Figure 2A shows the apraxic and the nonapraxic groups preprogrammed repetitive sequences similar to the control group, regardless of length ($F < 1.0$). For all subjects, sequence length had no effect on RTs. There was a trend for the mean RT of the entire left stroke group to be longer than the control group ($P < 0.06$), but there was no difference between the apraxic and the nonapraxic patients.

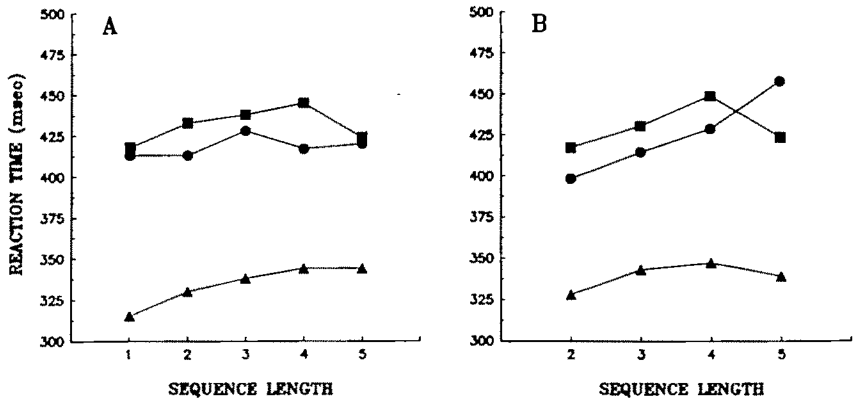

FIG. 2. Mean reaction times for repetitive (A) and heterogeneous (B) sequences. For repetitive sequences, standard errors of the mean averaged 55, 59 and 22 in the apraxic (●), nonapraxic (■) and control (▲) groups, respectively. For heterogeneous sequences, standard errors of the mean averaged 72, 51 and 20 in the apraxic, nonapraxic and control groups, respectively.

Heterogeneous sequences. Reaction times typically increase with sequence length when sequences consist of different movements because subjects construct a motor plan consisting of subprograms, one for each response in the sequence. However, because subjects may chunk or group a series of responses or complete some of the programming prior to the RT interval, nonlinear effects of sequence length on RT are often reported (Harrington and Haaland, 1987, 1991*a*,*b*). Figure 2B suggests that, for sequences containing different hand postures, RT increased more with increasing sequence length for the apraxic than the nonapraxic and the control groups. The supporting statistical analyses showed a group×length interaction [F(6,90) = 2.26, $P < 0.05$]. Follow-up analyses comparing the apraxic and the control groups revealed a significant group×length effect [F(3,66) = 3.37, $P < 0.025$], whereas no such interaction was found when comparing the nonapraxic and control groups. Trend analyses showed that sequence length had a linear effect on RTs in the apraxic group [F(1,6) = 6.38, $P < 0.05$]. By comparison, for both the nonapraxic and control subjects sequence length had a nonlinear affect on RTs [F(1,25) = 3.85, $P < 0.06$] such that RTs increase with length up to n = 4 and asymptote thereafter. Averaging across sequence length, mean RT of the entire left stroke group was longer than the control group ($P = 0.052$) but there was no difference between the apraxic and the nonapraxic patients.

Cognitive processing during movement

Repetitive sequences: inter-response times. To determine whether the execution of a single movement was more affected in the apraxic patients by the number of other responses within a sequence, not simply an individual hand posture, the effect of sequence length on each IRT was analysed. The difference between the shortest and longest sequence length was analysed for each IRT. Figure 3 displays the means for each IRT as a function of sequence length. There was a trend for the first IRT (IRT_1) to be slower for the entire left stroke group than for the control group ($P = 0.052$) and all IRTs for subsequent responses were significantly slower ($P < 0.025$). However, as

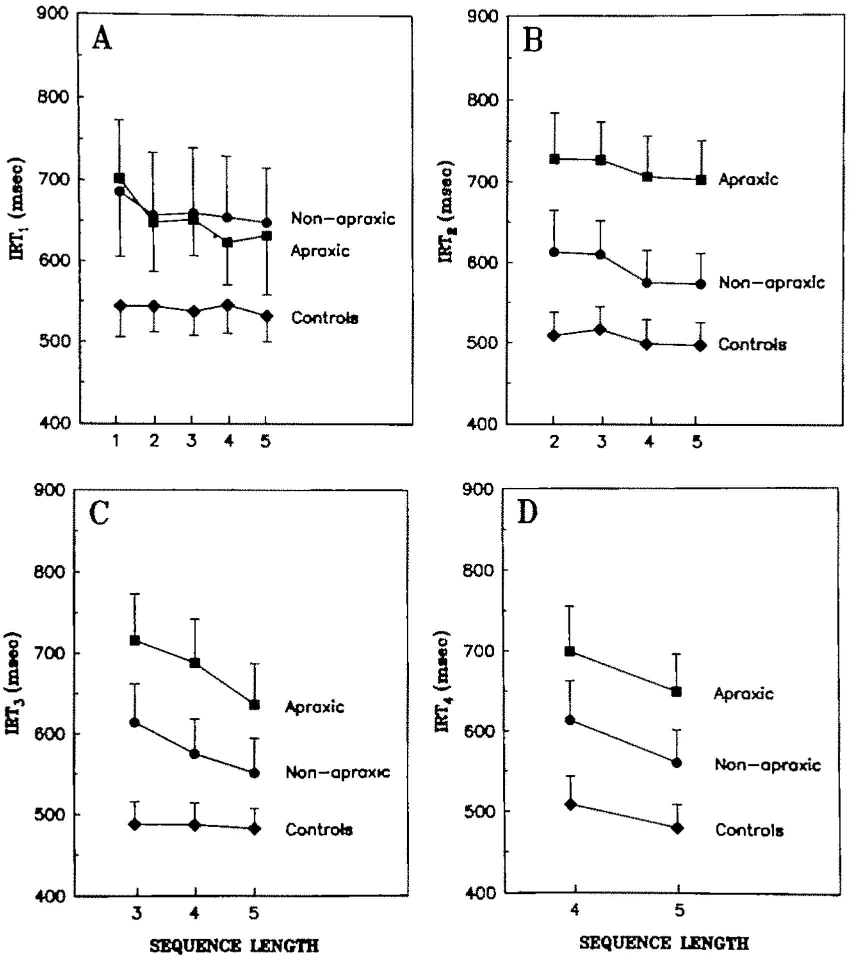

FIG. 3 Inter-response times (IRTs) for repetitive sequences as a function of sequence length. A, B, C, D represent the mean IRTs (plus standard error bars) for IRT_1, IRT_2, IRT_3 and IRT_4, respectively

can be seen in Fig. 3, the apraxic patients were not significantly slower than the nonapraxic patients. Figure 3A,C,D shows that IRTs changed with sequence length more for the two left stroke groups than for the control group. The supporting statistical analyses showed a group×length interaction for IRT_1 [$F(2,30) = 11.92$, $P < 0.01$] and IRT_3 [$F(2,30) = 11.13$, $P < 0.001$], and there was a trend for an interaction for IRT_4 [$F(2,30) = 2.01$, $P = 0.15$]. The pattern of sequence-length effects on IRTs was similar, however, for the apraxic and the nonapraxic patients. This observation was confirmed by the nonsignificant interactions of group (i.e. apraxic vs nonapraxic)×sequence length for each IRT ($F < 1.0$ for all IRTs). Thus, the execution of a single movement within a sequence was generally more affected by the number of other responses in a sequence for the apraxic and the nonapraxic patients than for the control subjects, suggesting both stroke groups engaged in more programming during movement.

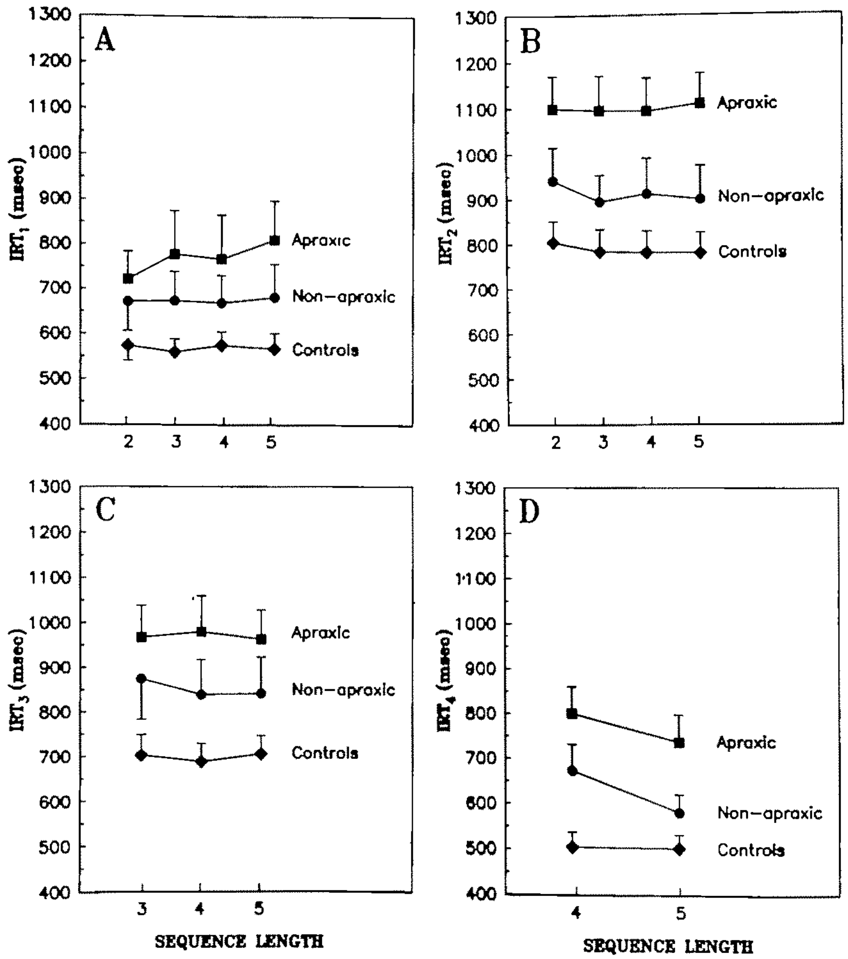

FIG. 4. Inter-response times (IRTs) for heterogeneous sequences as a function of sequence length. A, B, C, D represent the mean IRTs (plus standard error bars) for IRT$_1$, IRT$_2$, IRT$_3$ and IRT$_4$, respectively.

Heterogeneous sequences: inter-response times. For all IRTs, both left stroke groups were significantly slower than the control subjects regardless of sequence length ($P < 0.025$), but Fig. 4 shows the apraxic patients were not slower than the nonapraxic patients. Figure 4 also suggests that sometimes the pattern of IRTs varied with sequence length in a different way for the stroke patients than for controls. Sequence length had no reliable effect on IRT$_2$ or IRT$_3$ for any of the groups (Fig. 4B,C). However, there were significant interactions of group × sequence length for IRT$_1$ [F(2,30) = 5.38, $P < 0.01$] and IRT$_4$ [F(2,30) = 9.08, $P < 0.01$]. In Fig. 4A it appears that IRT$_1$ increased with sequence length but only for the apraxic group. Follow-up analyses comparing the apraxic and the control groups revealed a group × length interaction [F(1,22) = 11.27, $P < 0.01$], indicating that the duration of IRT$_1$ increased linearly as sequence length increased for the apraxic [F(1,6) = 5.86, $P = 0.052$] but not the control group

(F < 1). No such differences were found when comparing the nonapraxic and the control groups. For IRT_4 (Fig. 4D) the pattern of sequence length effects on IRTs was comparable in the apraxic and the nonapraxic groups. The different pattern of sequence length effects found for IRT_1 and IRT_4 most likely reflects the type of programming ongoing during sequencing. The IRT_1 increased with sequence length only in the apraxic group because programming that began during the RT interval was ongoing. This explanation is consistent with the finding of a greater increase in RT as a function of sequence length for the apraxic group. As for IRT_4, the fourth response was a repetition of a previous hand posture which explains why this pattern of findings was similar to those reported for repetitive sequences.

Movement time. The MT analyses, which focused on the execution time for the entire sequence, examined the relative difficulty of sequencing repetitive vs different hand postures as a function of sequence length. The time to execute a single hand posture was not significantly different between the apraxic (mean = 702, SEM = 71) and the nonapraxic patients (mean = 686, SEM = 80), but MT for a single hand posture was significantly longer for the entire left stroke group relative to the control group (mean = 544, SEM = 38) [F(1,31) = 5.4, $P < 0.05$]. Similarly, although MTs for sequences of hand postures were not significantly slower in the apraxic (repetitive: mean = 2377, SEM = 168; heterogeneous: mean = 3167, SEM = 214) than the nonapraxic patients (repetitive: mean = 2119, SEM = 178; heterogeneous: mean = 2694, SEM = 221), the entire left stroke group executed sequences more slowly than the control group (repetitive: mean = 1783, SEM = 97; heterogeneous: mean = 2257, SEM = 127) ($P < 0.01$).

To control for the possibility that MT differences among groups on sequences could

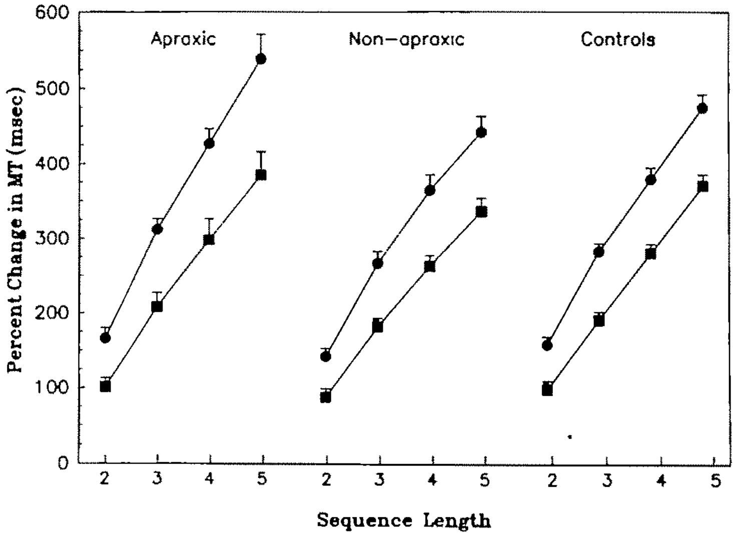

FIG. 5. The mean percentage change (plus standard error bars) in movement time (MT) for repetitive (■) and heterogeneous (●) sequences. Percentage values were calculated using the following formula $(MT_n - MT_1)/MT_1$ where n represents a particular sequence length and MT_1 is the time to execute a single hand posture.

be due to the cumulative effects of slower execution times for a single posture, the percentage increase in MT for sequences relative to the time to execute a single posture was analysed. When MTs were corrected for baseline performance of single postures there was an interaction of group×sequence type×sequence length [F(6,90) = 2.62, $P <$ 0.025]. Figure 5 suggests that this interaction was due largely to performance differences in the apraxic group, especially on heterogeneous sequences. The supporting statistical analyses showed that sequence type and sequence length had similar effects on adjusted MTs for the nonapraxic and the control groups. In contrast, for repetitive sequences the apraxic group did not differ from the nonapraxic or the control groups in the percentage change in MT as a function of sequence length. However, for heterogeneous sequences comparisons among the three groups revealed a group×length interaction [F(6,90) = 3.42, $P < 0.01$], indicating that MTs increased much more rapidly with sequence length for the apraxic group relative to both the nonapraxic group [F(1,14) = 9.53, $P < 0.01$] and the control group [F(1,22) = 5.78, $P < 0.05$]. In addition, the apraxic patients showed a greater difference in MT between the two sequence types relative to the nonapraxic patients [F(1,14) = 5.84, $P < 0.05$] and the normal control subjects [F(1,22) = 5.82, $P < 0.05$]. This effect, however, was specific to longer sequences such that the apraxic group showed greater differences between the two sequence types only when sequences contained four or five postures [apraxic vs nonapraxic group: n = 4 F(1,14) = 2.62, $P = 0.12$ and n = 5 F(1,14) = 9.58, $P < 0.01$; apraxic vs control group: n = 4 F(1,22) = 4.48, $P < 0.05$ and n = 5 F(1,22) = 8.02, $P < 0.01$]. These findings demonstrated that only the apraxic group had difficulty executing longer sequences of heterogeneous postures which did not involve additional changes between different hand postures, only a repetition of a preceding posture.

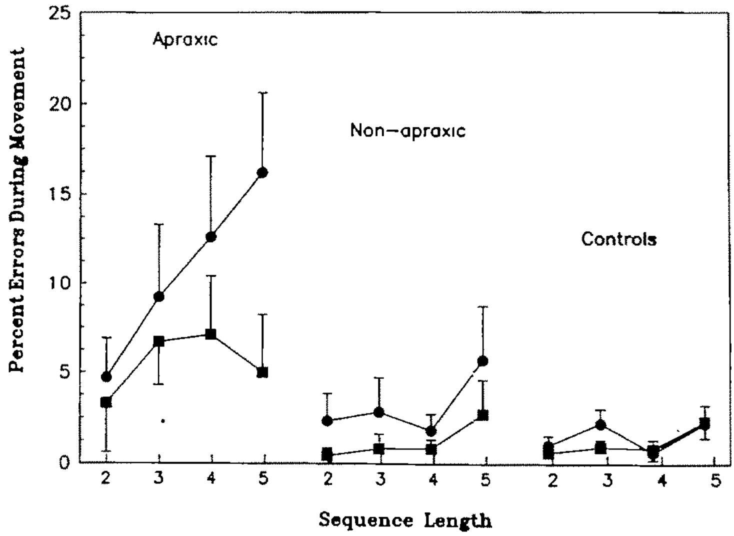

FIG. 6. The mean percentage errors (plus standard error bars) during movement for repetitive (■) and heterogeneous (●) sequences.

Errors during movement. The analyses of the percentage errors during movement compared group differences in error rates and, most importantly, showed whether the group differences varied depending on sequence type or length. Error rates for a single hand posture were not significantly different among the groups (apraxic: mean = 3.5, SEM = 2.3; nonapraxic: mean = 2.4, SEM = 0.8; control: mean = 0.9, SEM = 0.4), although there was a tendency for all of the left stroke patients to make more errors on a single posture than controls ($P < 0.10$). Figure 6 shows that the percentage errors generally increased for all subjects as sequences became longer but primarily for heterogeneous sequences, and especially for the apraxic patients. The supporting statistical analyses showed an interaction of group × sequence type × sequence length [F(6,90) = 3.65, $P < 0.01$]. Planned comparisons showed that for repetitive sequences the pattern of errors did not vary among the three groups as a function of sequence length, although Fig. 6 shows there was a trend for errors to increase with length more in the apraxic than the control group [F(3,66) = 2.63, $P = 0.057$]. No such trends were found in the nonapraxic group (F < 1). For heterogeneous sequences, comparisons among the three groups showed a group × length interaction [F(6,90) = 4.34, $P < 0.001$] such that there were no differences between the nonapraxic and the control groups in error rates, regardless of sequence length (F < 1). However, errors increased more with increasing sequence length for the apraxic group relative to both the nonapraxic group [F(3,42) = 2.81, $P = 0.05$] and the control group [F(3,66) = 10.05, $P < 0.001$]. In addition, the apraxic group showed a greater increase in errors for heterogeneous sequences, but only for those containing four [apraxic vs nonapraxic: F(1,14) = 2.07, $P = 0.17$; apraxic vs control: F(1,22) = 6.71, $P < 0.025$] and five hand postures [apraxic vs nonapraxic: F(1,14) = 4.73, $P < 0.05$; apraxic vs control: F(1,22) = 15.29, $P < 0.01$]. No such differences between sequence types were found between the nonapraxic and the control groups. These findings parallel the MT results as sequencing was disrupted in the apraxic but not the nonapraxic patients largely on heterogeneous sequences consisting of four or five responses.

Relationship between sequencing and cognitive status

Apraxia severity was correlated with auditory comprehension ($r = -0.64$), verbal fluency ($r = 0.65$) and visuospatial skills ($r = 0.58$), such that poorer language and spatial skills were related to more severe apraxia, accounting for 34–41% of the variance. Although auditory comprehension and verbal fluency were highly correlated ($r = -0.80$), neither of these tests was related to visuospatial skills ($r = -0.09$ and $r = 0.30$ for auditory comprehension and verbal fluency, respectively) indicating a separate underlying visuospatial component to apraxia. These findings raise the question as to whether the pattern of sequencing differences between the apraxic and nonapraxic patients might vary depending upon these measures, especially as the apraxic group was significantly impaired relative to the nonapraxic group on auditory comprehension and visuospatial skills. To examine this, separate regression analyses were conducted, analysing the relationships between the Token Part V, the Cookie Theft and the Block Design subtests and RTs, IRTs, adjusted MTs and errors for repetitive and heterogeneous sequences. The interaction of an ancillary test with group and sequence length was of interest. The results reported in this section are exploratory and preliminary, and should be interpreted with caution as the sample sizes were small, multiple statistical tests were conducted and the majority of patients were not clinically impaired on the ancillary tests.

Despite the differences between the two stroke groups in auditory comprehension and visuospatial skills, these tests did not interact with group, sequence length or sequence type for any measures, indicating that group differences on these tests could not explain the pattern of findings for the apraxic and the nonapraxic groups. However, there was a significant verbal fluency×group×length interaction [$F(3,36) = 4.13$, $P < 0.025$]. Follow-up analyses showed poorer verbal fluency was correlated with greater increases in error rates for sequences containing two vs five responses for both groups (apraxic $r = -0.65$; nonapraxic $r = -0.66$). However, as sequence length increased from two to five postures, apraxic patients with normal fluency ($n = 3$; fluency $= 6.5 \pm 0$) or impaired fluency ($n = 4$; fluency $= 4.1 \pm 2.7$) showed similar increases in error rates (9.4% and 13.1%, respectively). In contrast, error rates increased more for the nonapraxic patients with impaired fluency ($n = 5$; fluency $= 5.9 \pm 0.4$) than for those with normal fluency ($n = 4$; fluency $= 6.7 \pm 0.2$) (6% and 0%, respectively). These findings show that, while better verbal fluency was associated with smaller changes in error rates with increasing sequence length in both groups, the apraxic group still showed a greater increase in error rates with longer sequences regardless of the fluency rating.

Computerized tomography analyses

Table 2 presents the lesion volume and location measurements for the apraxic and the nonapraxic groups. While Table 2 suggests that the apraxic patients had somewhat larger lesion sizes than the nonapraxic patients, Mann-Whitney U tests showed no significant group differences. Only three of the apraxic patients had lesion sizes greater (4.4%, 6.1%, 12%) than the largest lesion size found in the nonapraxic group, and in the remaining apraxic patients lesions occupied <1.7% of the total brain volume. Also there were no reliable differences between the apraxic and the nonapraxic groups on the linear and volumetric measures of lesion location.

TABLE 2. LESION VOLUME AND LOCATION FOR THE APRAXIC AND THE NONAPRAXIC GROUPS

	Apraxic group			*Nonapraxic group*		
	Mean	*(SD)*	*Range*	*Mean*	*(SD)*	*Range*
Lesion volume[1]	3.8	(4.2)	0.1–12.0	1.3	(1.3)	0.1–3.7
Anterior lesion volume[2]	48.5	(40.4)	0–97	58.1	(45.5)	1–100
Posterior lesion volume[2]	51.5	(40.4)	3–100	41.9	(45.5)	0–100
Anterior distance[3]	41.3	(17.1)	22–68	40.0	(15.5)	14–68
Posterior distance[3]	26.1	(21.4)	1–50	38.2	(20.5)	0–53

[1] Lesion volume is proportional to the total brain volume

[2] The volumetric measurements reflect the proportion of the lesion that is located anterior or posterior to the midpoint between the frontal and occipital poles, and are proportional to the total lesion volume.

[3] The linear measures are proportional to the total distance from the frontal to the occipital pole A smaller proportion indicates that the lesion is located closer to the frontal or occipital pole

DISCUSSION

The results showed deficits in some levels of programming were general to left hemisphere damage, whereas others were specific to the disorder of ideomotor limb apraxia. All patients with left hemisphere damage exhibited deficits in initiating the sequence (i.e. slower RTs), executing single postures and controlling individual movements during sequencing. Only the apraxic patients showed a disruption in programming heterogeneous sequences prior to and during movement, but only for longer sequences. These findings could not be attributed to motor slowness because there were no differences between the apraxic and the nonapraxic patients in absolute RTs, IRTs or MTs. Also the findings were not related to lesion size, quantified measures of lesion location or auditory comprehension deficits. Although poor verbal fluency was associated with greater increases in error rates with increasing sequence length, these increases were greater in the apraxic group, regardless of whether the patients were fluent or not. Thus, language deficits cannot entirely explain the different pattern of sequencing abnormalities found between the apraxic and the nonapraxic groups. This is consistent with other studies showing poor gesture learning and gesture comprehension deficits in apraxic-aphasic but not nonapraxic-aphasic groups (Rothi and Heilman, 1984; Rothi *et al.*, 1985).

Cognitive deficits general to left hemisphere damage

Encoding deficit. The conceptualization of apraxia as a motor programming disorder has a long tradition, yet the specific nature of the hypothetical programming deficit has been both controversial and elusive. Two studies using the selective reminding method (Buschke and Fuld, 1974) reached different conclusions about the processes underlying gestural learning deficits in apraxia. Faglioni *et al.* (1990) reported that apraxia was a deficit specific to encoding and storage, but not retrieval. In contrast, others have found storage but not encoding or retrieval problems in aphasic-apraxic and aphasic-nonapraxic patients (Rothi and Heilman, 1984). In our study, RTs of the apraxic and the nonapraxic groups were slower (regardless of sequence length or type) than the control group which may point to an encoding deficit with left hemisphere damage, although response initiation deficits cannot be ruled out.

Generating spatiotemporal memory codes. After assembling a motor plan, additional cognitive computations must be engaged to translate the plan into physical movement. These computations most likely involve many levels of programming. Inter-response times of single movements and individual postures within repetitive or heterogeneous sequences were equally slowed in the apraxic and the nonapraxic groups. Spatial orientation and location deficits with left hemisphere damage (Rothi *et al.*, 1988; Poizner *et al.*, 1990) could underlie slowed IRTs for individual movements if a deterioration in spatiotemporal codes results in difficulties generating the motor patterns for individual postures.

Scheduling/timing movements. At a different level of analysis, the negative relationship between IRTs and sequence length for repetitive sequences and for IRT_4 of heterogeneous sequences suggested both stroke groups continued to engage in programming concerning the sequence, not simply an individual hand posture. One possible explanation for this pattern of findings is that left hemisphere damage disrupts the ability to schedule efficiently motor programs for individual movements within a sequence (Harrington and Haaland, 1991*a*). Specifically, before activating the physical parameters of a response other cognitive computations are likely to be required, such as scheduling when to execute a response. For instance, each response in a sequence may be associated with an absolute time at which to execute the movement. When sequences contain repetitive movements, subjects normally either apply the same timing rule to all responses or time all responses simultaneously so that the length of a sequence has no effect on IRTs. When timing is dysfunctional, it proceeds more serially. Scheduling movements may be postponed to ensure that the computations of when a response will be initiated coincides with the activation of the physical parameters of the response, minimizing as much as possible prolonged delays between individual responses. Thus, patients with left hemisphere damage initiate movements contained in longer sequences faster because they have more time to complete the scheduling of the remaining postures in the sequence while executing the preceding postures. With shorter sequences, response execution is delayed because cognitive operations occur closer in time and must be at least partially completed before the activation of any particular hand posture. The proposed timing deficit is consistent with mounting evidence from studies of brain-damaged adults, language-impaired children, and neurologically intact subjects showing the left hemisphere is superior to the right hemisphere in the efficiency of processing rapid, temporal information (*see* Hammond, 1982; Tallal, 1983; Tzeng and Wang, 1984).

Cognitive deficits specific to apraxia

Preprogramming sequences. Only the apraxic group showed deficits in assembling a motor plan prior to movement for heterogeneous sequences. This first phase of planning presumably involves identifying and retrieving the subprograms for each response or response unit. Reaction times for heterogeneous sequences increased linearly with sequence length in the apraxic group, whereas in the nonapraxic and control groups there was a nonlinear effect. [In all groups the magnitude of sequence length effects on RT was very small. This was expected because the effect of sequence length diminishes when the interval prior to the imperative stimulus is 1 s or longer (Klapp *et al.*, 1974; Harrington and Haaland, 1991*b*). This is because subjects can plan much of the response before the imperative stimulus.] The first IRT also increased with sequence length, but only in the apraxic group, indicating the apraxic patients continued to engage in preprogramming while executing the first response. Because the form (i.e. linear vs nonlinear), but not the slope, of the RT function differed in the apraxic group a retrieval deficit account of the apraxic group's data is less likely. This is consistent with other studies (Rothi and Heilman, 1984; Faglioni *et al.*, 1990). A more plausible explanation is that the nonlinear effect of length on RT for heterogeneous sequences in the nonapraxic and control groups may reflect organizational strategies. For example, in a sequence of four responses (e.g. PBPP) subjects may treat each response as a unit which explains the linear increase in RT between n = 2 and n = 4. However, for sequences containing five responses (e.g. PBPPP) subjects may treat each of the first three responses as individual units (e.g. PBP) and the last two as a single unit (e.g. PP), accounting for the asymptote in RT after four postures. Of course, other organizational strategies are possible. In contrast, the linear RT function in the apraxic patients may reflect their tendency to plan each posture in the sequence as a unit, neglecting to chunk or parse the sequence when it is longer. This interpretation may be the most parsimonious account of the RT results as we now consider the pattern of MTs and errors in the apraxic patients.

Temporal organization. Do the proposed abnormalities with left hemisphere damage as inferred through the IRT findings also underlie the MT and error findings in the present study? This does not appear to be the case as only the apraxic group showed a greater increase in MTs and error rates as heterogeneous sequences increased in length despite showing the same impairments as the nonapraxic group in IRTs. This dissociation suggests a different mechanism supports sequencing skills separate from those linked to timing responses or generating visuospatial memory codes.

We embrace an interpretation of the MT and error results which links it to the RT findings. Specifically, the execution of a sequence is dependent upon the way in which it is organized prior to movement (Rosenbaum *et al.*, 1983). Actions are normally parsed into natural rhythmic or spatial groupings which facilitate the development of skilful behaviours (Povel and Collard, 1982). Apraxia may produce a breakdown in parsing so that organizing principals for grouping responses are disrupted. This may explain why apraxics can normally execute shorter sequences of heterogeneous postures, whereas their performance breaks down on longer sequences, those which could benefit most from a parsing mechanism. In addition, abnormalities in cognitive computations that support parsing should lead to impaired learning which is consistent with deficient learning of hand position sequences or of gestures with left hemisphere damage (Rothi and Heilman, 1984; Jason, 1985; Rothi *et al.*, 1988).

An alternative explanation for the above findings, that apraxia produces a deficit specific to controlling changes in different postures (Kimura, 1977), is not satisfying for two reasons. First, IRTs of the apraxic and nonapraxic groups were slowed equally for repetitive and heterogeneous sequences. Secondly, the apraxic group showed deficits only on heterogeneous sequences containing four or five postures (e.g. PBPP, PBPPP) which consisted of the same number of different hand postures as those containing three postures (e.g. PBP), except for an addition of a repeated posture(s) at the end of the sequence. The MT and error findings, however, cannot rule out the possible role of serial ordering deficits in apraxia. Although little direct evidence exists linking ideomotor limb apraxia to a serial ordering deficit (Kimura and Archibald, 1974; Kimura, 1977; Jason, 1985, 1986), this issue deserves further study as the serial ordering requirements of most tasks, including ours, have been minimal, due to the use of highly practised gestures or sequences containing a limited number of responses.

Summary remarks

The present study, together with previous investigations of sequencing in patients with right hemisphere damage and Parkinson's disease (Harrington and Haaland, 1991*a,b*), provide some preliminary clues about several basic and functionally separate cognitive computations that may underlie motor sequencing. In addition, some of these computations appear to be most efficiently carried out by different neural subsystems. This is consistent with MacKay's (1985) theory of action which distinguishes among levels of cognitive-motor function (i.e. representations of actions, timing processes, sequential processes and parsing mechanisms), and predicts apraxia and other motor disorders result from damage to selected neural subsystems.

Prior to movement, encoding of single postures and sequences was slowed in left hemisphere apraxic and nonapraxic patients. Previous sequencing studies have not uncovered such deficits in patients with right hemisphere damage (Harrington and Haaland, 1991*a*) or Parkinson's disease (Harrington and Haaland, 1991*b*), which shows such deficits are not simply general to brain damage.

The apraxic and nonapraxic groups' problems executing single postures or individual postures contained within a repetitive or a heterogeneous sequence have not been observed in other neurological disorders such as Parkinson's disease (Harrington and Haaland, 1991*b*). Specifically, parkinsonian patients displayed slowed IRTs and greater error rates when executing changes between different hand postures, but generally not when executing repetitions of the same posture (Harrington and Haaland, 1991*b*). This may suggest that processes controlling transitions between different postures (e.g. changes in force production) are regulated more directly by the basal ganglia system, whereas the left hemisphere is specialized for higher level cognitive computations concerned with generating spatiotemporal codes for movements.

The present results emphasized the left hemisphere's efficiency in temporal processing. This is consistent with a large literature examining the perception and production of time in neurologically intact individuals and in patients with damage to the left hemisphere (*see* Hammond, 1982). However, the assertion that timing mechanisms are specific to the cerebral cortex of the left hemisphere is likely to be an oversimplification, as left hemisphere damage resulting from stroke or developmental disabilities typically involves subcortical damage or, at minimum, a disconnection of cortical and subcortical systems. In fact, using a similar sequencing task we found sequence length had negative effects on the IRTs of repetitive sequences in patients with Parkinson's disease (Harrington and Haaland, 1991*b*), which is consistent with other reports of central timing deficits in these patients (Wing *et al.*, 1984; Poizner, 1990). Thus, timing mechanisms for movement may be an emergent property of left cerebral cortex and basal ganglia interactions. The cerebellum, however, is also involved in timing operations, particularly as they concern the measurement or perception of time (Keele and Ivry, 1990). Further research into temporal aspects of movements is needed to determine whether perception of time, reproduction of time intervals and scheduling movements in sequences involve functionally separate cognitive computations which engage different neural subsystems.

Dysfunctional temporal organization processes, as inferred through the RT, MT and error data, were specific to the disorder of apraxia. Interestingly, such deficits have not been observed in patients with Parkinson's disease (Harrington and Haaland, 1991*b*). In these patients, RTs for heterogeneous sequences increased with length up to four responses and then reached an asymptote similar to control subjects. However, the slope of this function is reduced relative to a control group, suggesting that basal ganglia abnormalities affect the ability to preprogram movement sequences completely. In addition, MTs and error rates in parkinsonian patients were normal regardless of sequence length or type. These findings are consistent with the low incidence of apraxia in Parkinson's disease (Sharpe *et al.*, 1983), and further point to the specificity of dysfunctional temporal organization in movement in the disorder of ideomotor limb apraxia. Direct tests of the proposed parsing deficits in these patient groups is one focus of our ongoing investigations in this area.

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PERFORMANCE OF REPETITIVE WRIST MOVEMENTS IN PARKINSON'S DISEASE

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SUMMARY

The timing of repetitive alternating 80 degrees flexion-extension movements of the right wrist was studied in 42 patients with Parkinson's disease, tested while not receiving dompaminergic medication and 20 age- and sex-matched controls. Five rates of movement (0.5 Hz, 1 Hz, 1.5 Hz, 2 Hz, 2.5 Hz) were examined. The interval between two successive flexion movements, as measured from the electromyography (EMG) records was taken as the unit of analysis or inter-response interval (IRI). At 0.5 Hz, 1 Hz and 1.5 Hz there were no differences between groups in mean IRIs. At higher rates of movement (2 Hz and 2.5 Hz), however, the controls were significantly more accurate in timing of repetitive movements than the patients. At all five frequencies, the patients with moderate or severe Parkinson's disease were less accurate in timing of repetitive movements than those with mild disease, although the differences were not significant. In nine patients tested in the 'on' and 'off' medication states, administration of 250 mg of levodopa/carbidopa resulted in significantly more accurate timing of repetitive movements. Wing and Kristofferson's (1973*b*) two-process model of repetitive movements was applied to the IRI data. At various rates of movement, the primary prediction of the model that lag 1 autocorrelations should be in the 0 to −0.5 range was violated in 40–70% of the patient and controls. For those subjects who had lag 1 autocorrelations in the expected range, IRI variability was to break down into a timekeeper and a motor delay variance. At all frequencies, the patients had significantly higher variance for IRI, timekeeper and motor delay than the controls. Although not significant, more severe Parkinson's disease was associated with greater IRI, timekeeper and motor delay variance, while administration of levodopa resulted in reduction of the three types of variance. The validity of the Wing and Kristofferson model for the analysis of this type of movement is discussed.

INTRODUCTION

Bradykinesia is one of the most striking symptoms of Parkinson's disease. In patients with this disorder, during ballistic movements the size of the first agonist burst is quantitatively reduced, thereby requiring additional cycles of alternating agonist/antagonist activation for completion of the movement (Hallett and Khoshbin, 1980). Although, the failure to sufficiently activate the agonist muscle may constitute a physiological mechanism for the hypometric feature of bradykinesia, it does not, however, constitute a sufficient explanation or the slowness of movement initiation in patients with this disorder. As noted by Hallett and Khoshbin (1980) muscle 'energizing' and 'timing' processes can be considered as separate functions, and 'a defect in energizing muscle need not be accompanied by a defect in muscle timing'. A similar conclusion was arrived

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at from the study of isometric force production instead of isotonic ballistic movements in Parkinson's disease by Stelmach and Worringham (1988). These authors noted that patients with Parkinson's disease are deficient in the regulation of force and time parameters, rather than simply in force production. As noted by Stelmach and Worringham (1988), timing is a primary aspect of any movement, since very few real life acts can be characterized by force attainment criteria independent of timing, and most tasks demand the production of an appropriate force-time pattern.

The problems encountered by patients with Parkinson's disease in the performance of simultaneous and sequential movements are well documented (Schwab *et al.*, 1954). Experimental evidence has shown that alterations of the relative timing of different movement components (Benecke *et al.*, 1986, 1987) is mainly responsible for the additional difficulty and extra slowness of these patients on simultaneous and sequential movements. Evidence for deficits in the timing of movement in Parkinson's disease has also been provided from reaction time studies (Evarts *et al.*, 1981; Bloxham *et al.*, 1984; Stelmach *et al.*, 1986; Sheridan *et al.*, 1987). Across these studies the reaction times of Parkinson's disease patients are slower than those of controls.

Generation and maintenance of a rhythm has been regarded as a possible strategy for timing of repetitive sequential movements (Martin, 1972). Reports of an inability of patients with Parkinson's disease to maintain a specific rhythm in tapping (Nakamura *et al.*, 1978; Nagasaki and Nakamura, 1982; Wing *et al.*, 1984; Keele and Ivry, 1987; Ivry and Keele, 1989) is also consistent with the suggestion of a deficit in timing.

The above evidence underlies the fact that an abnormality in the specification or production of the timing parameter of movement may play a prominent role in bradykinesia (Artieda *et al.*, 1992; Pastor *et al.*, 1992). In fact it has been proposed that the slowness of movement in Parkinson's disease may be a result of the dysfunction of an hypothetical timekeeper (Wing and Miller, 1984; Wing *et al.*, 1984).

Wing and Kristofferson (1973*b*) proposed a two-process model of the analysis of the timing of repetitive movements. In this model two independent processes are assumed to be involved in timing of repetitive movements. The first is an internal timekeeper which triggers the response and so determines when a response should be made, and the second is an implementation system which executes the motor command. According to this model, repetitive movements are performed in an open-loop fashion, such that the timekeeper triggers a response without reliance on feedback from the preceding response.

The variability of the inter-response interval (IRI) is considered to be a sum of the variability of the internal timekeeper and the motor implementation system. Each IRI can be calculated as the sum of a timekeeper interval plus the difference in motor delays associated with any one response and the preceding one (Fig. 1). Therefore, the interval between two successive overt responses, R_{j-1} and R_j can be calculated from:

$$I_j = C_j + D_j - D_{j-1}$$

where I_j, C_j, D_j and D_{j-1} represent the IRI, the timekeeper interval, the motor delay associated with R_j and delay associated with R_{j-1}, respectively. Given the independence

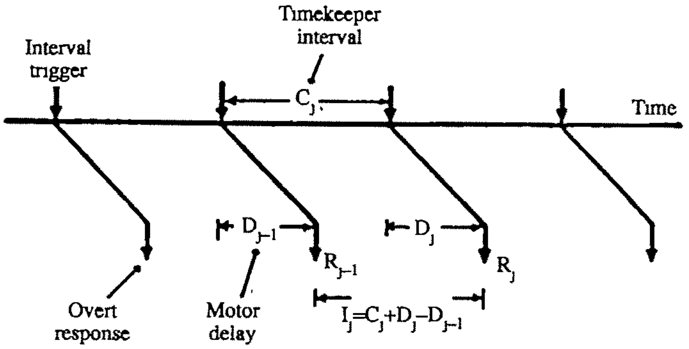

FIG 1 Diagram showing the mathematical model of Wing and Kristofferson (1973*b*) for the analysis of repetitive movements. I_j = inter-response interval; C_j = timekeeper interval; D_j = motor delay.

of the two sources of variance, the variance of IRI can be calculated from the data as follows:

$$\sigma_I^2 = [\Sigma_{j=1} (I_j - I)^2]/n \tag{1}$$

The variance of motor delay is, in turn, obtained from the analysis of the variability of one interval in relation to the preceding one according to:

$$\sigma_D^2 = -\text{autocov} = [\Sigma_{j=2} (I_j - I)\ (I_{j-1} - I]/n-1 \tag{2}$$

The model predicts that lag 1 autocorrelations between adjacent intervals will be in the range of 0 to −0.5. Once the variance of IRI and motor delay have been calculated from Equations 1 and 2, the timekeeper variance can be calculated through subtraction using the following equation:

$$\sigma_C^2 = \sigma_I^2 - 2\sigma_D^2$$

Wing *et al.* (1984) studied repetitive tapping with the index finger of each hand in a female hemiparkinsonian patient. The analysis of the IRIs was carried out by means of the Wing and Kristofferson (1973*b*) model. An increased clock variability on the affected side in comparison with the unaffected hand was found. The variability of the motor implementation estimate was, however, found to be similar for the two hands. From this a deficit in internal activation of a preplanned movement due to dysfunction of the internal timekeeper was inferred.

The results of this study also suggest that both hemispheres have timekeeping capabilities which are at least partially independent. This conclusion is based on the observation of unilateral timing deficits when comparing affected and unaffected hands and is also supported by the single or multiple case studies of Ivry *et al.* (1988) and Ivry and Keele (1989) with patients with Parkinson's or cerebellar disease showing that the timing mechanisms for one hand can be damaged without affecting the performance of the other hand.

Ivry and Keele (1989) used the model of Wing and Kristofferson (1973*b*) in a controlled group study of repetitive finger tapping at regular intervals of 550 ms. The patients with Parkinson's disease had mean IRIs significantly shorter than the elderly controls. However, in terms of the IRI variance, the Parkinson's disease patients and the elderly controls did not differ, while the patients with cerebellar disease and those with cortical lesions were significantly impaired compared with the parkinsonian patients and elderly controls, despite being younger. The variability of the inter-tap interval was further decomposed using the above model. The cerebellar group had significantly higher timekeeper and motor delay estimates compared with the parkinsonian patients and the elderly controls. The difference between the parkinsonian patients and the elderly controls was only in terms of the timekeeper variability. The latter result is in contrast with those of an earlier study by Keele and Ivry (1987) which investigated the effects of levodopa medication on finger tapping in a single case study with a 75-yr-old parkinsonian patient. The patient was tested shortly following diagnosis in a drug naive state and on several occasions following administration of levodopa medication. While motor delay estimates remained fairly constant throughout the study, the clock variance estimates were significantly reduced following medication. It was concluded that the major effect of basal ganglia dysfunction in Parkinson's disease was on the operation of the internal timekeeper and that medication can correct the deficits in the timing process.

In light of the discrepancies in the findings of Keele *et al.* (1987) and Ivry and Keele (1989) for patients with Parkinson's disease, the aim of the present study was to examine the performance of repetitive rhythmic movements in the presence of external auditory feedback and when such rhythmic movements were self-paced in patients with Parkinson's disease compared with normal controls. The effects of rate of movement, the degree of severity of Parkinson's disease and the medication status of the patients on performance were also assessed.

METHODS

Subjects

Forty-two (28 males, 14 females) patients with idiopathic Parkinson's disease were tested. None of the patients had any clinical evidence of dementia or depression. All patients had scores within the normal range (above 25) on the Mini Mental Test (Folstein *et al.*, 1975). None of the patients had severe dyskinesias or painful dystonic cramps that could interfere with performance of the experimental tasks. The mean age of the patients was 57.4 yrs (SD = 9.5). The mean age of onset of Parkinson's disease was 49.9 yrs (SD = 12.3). The duration of the illness ranged from 8 mths to 26 yrs, with an average of 7.4 yrs (SD = 5.9).

On the basis of their response to levodopa therapy, the patients were classified into mild, moderate and severe disease groups. The 15 patients in the middle group had a good response to levodopa. The patients in the moderate category (n = 22) had simple 'wearing off' fluctuations and end-of-dose deterioration. The five patients with severe disease showed complex fluctuations indicated by end-of-dose deterioration, 'off' periods resistant to levodopa therapy and presence of dyskinesia. Severity of the disorder was also quantified using the King's College Hospital (KCH) Parkinson's disease rating scale (range 0–117, higher scores indicate more severe disease). The mean KCH scores for the clinically defined mild, moderate and severe groups were respectively 18.7 (SD = 7.7), 39.4 (SD 13.3) and 58 (SD = 16.6). The average age of the patients with mild, moderate or severe Parkinson's disease was respectively 58.3 yrs (SD = 10), 56.9 yrs (SD = 9.8), and 56.8 yrs (SD = 7.8). The corresponding duration of illness for the three subgroups was respectively 2.7 yrs (SD = 1.9), 9.8 yrs (SD = 5.9) and 11.2 yrs (SD = 5.8).

All 42 patients were studied in the 'off' state 48 h after withdrawal of levodopa therapy. Nine of the patients also performed the experimental tasks in the 'on' state, following administration of 250 mg of levodopa/carbidopa on a second occasion, 3 d after the first.

A group of 20 normal controls (13 males, seven females), the majority of whom were the patients' relatives were also tested. Their mean age was 57 yrs (SD = 10.8). None of the normal controls had a history of head injury or physical or neurological illness. All patients and controls were right-handed.

Procedure

The experimental task involved 80 degrees flexion-extension movements of the right wrist. The subject was seated with the shoulder abducted, the elbow flexed 90 degrees, and the forearm semi-pronated and resting on a U-shaped aluminium plate. The amplitude of the flexion-extension movements was indicated by an 80 degree angle drawn on the surface of the aluminium plate. Surface electromyography (EMG) was recorded from the flexor and extensor carpi muscles of the forearm. The angular displacement of the wrist was measured by a potentiometer (Fig. 2). Electromyographic activity and wrist position were recorded 'on line'.

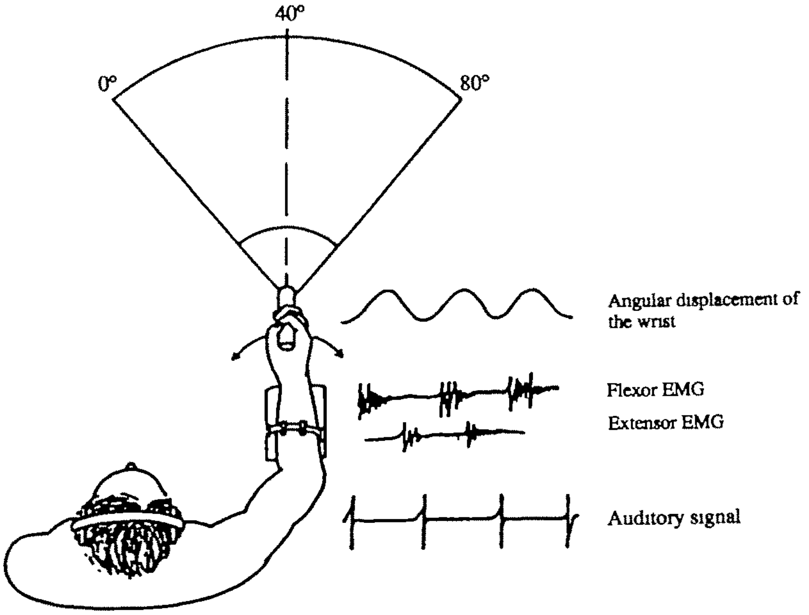

FIG 2. Schematic presentation of the method of recording ballistic movements of the wrist.

Each trial began with a series of 30 tones (80 dB) each 1 ms in duration, presented binaurally through headphones. The subject was asked to begin with a flexion movement of the wrist followed by an extension and to continue the flexion-extension movements in synchrony with the auditory stimuli. Furthermore, the subject was instructed to continue the 80 degrees flexion-extension movements of the wrist at the same rate after the tones stopped. The block of trials ended when 30 self-paced movements had been performed after cessation of the tones. The tones were presented at five different frequencies: 0.5 Hz, 1 Hz, 1.5 Hz, 2 Hz and 2.5 Hz. All subjects performed blocks of trials in the same fixed order, beginning with the slowest and ending with the fastest rate of presentation To allow the subjects to 'internally' establish the required rate of movement for both the externally (tone) and self-paced conditions, the data from the first five movements of the trial were discarded and the analyses were performed on the remaining 25 flexion-extension movements. The various measures derived from the data are shown in Fig. 3. Using the angular displacement data, the time interval between the onset of two flexion movements, two extension movements, a flexion and the next extension, an extension and the subsequent flexion were calculated. Similar measures were derived using the flexor and extensor EMG data.

In addition, to obtain information about individual 'limits', subjects were asked to perform 30, 80 degrees flexion-extension movements of the wrist at their personally maximal rate. Speed of movement initiation and execution was assessed by performance of a 40 degrees flexion movement of the wrist in response to an auditory stimulus. The average simple premotor reaction times (time from the onset of EMG activity) and movement execution times across 20 trials were calculated.

RESULTS

The interval between two successive flexion movements was considered as a complete motor cycle and was therefore used as the unit of analysis for IRIs. As expected from the matching procedure, the patients with Parkinson's disease and the controls showed no differences in terms of age (t = 0.15, d.f. = 60, P = 0.88), or sex distribution (χ^2 = 1.1, d.f. = 1, P = 0.28).

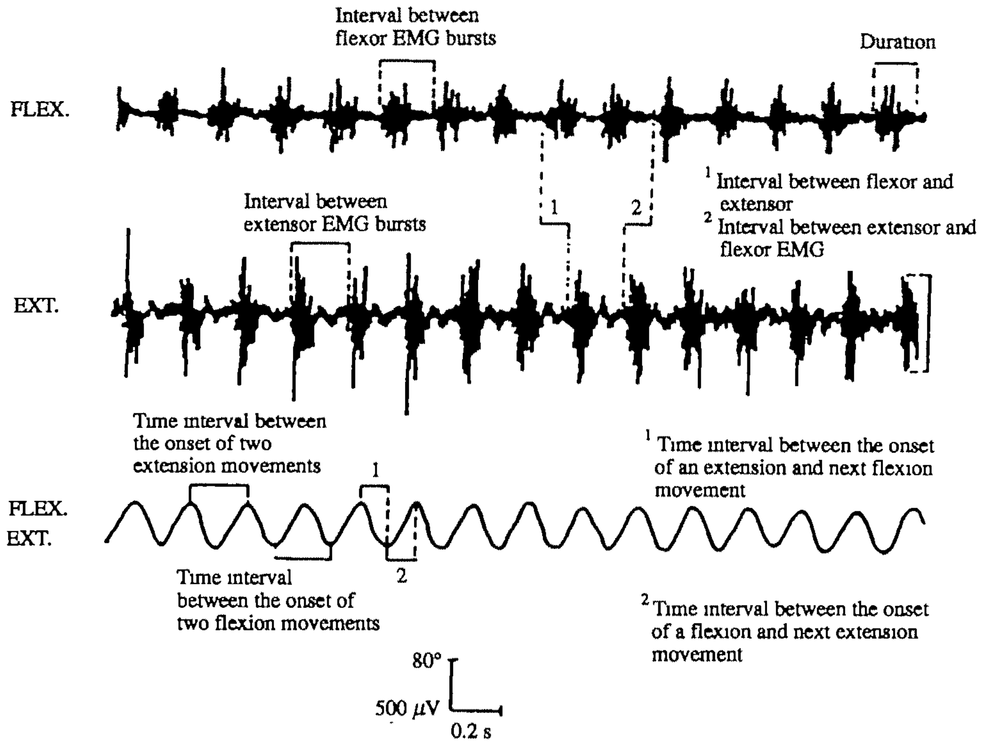
Interval between flexor EMG bursts
Duration
FLEX.
[1] Interval between flexor and extensor
[2] Interval between extensor and flexor EMG
1
2
Interval between extensor EMG bursts
EXT.
Time interval between the onset of two extension movements
1
[1] Time interval between the onset of an extension and next flexion movement
FLEX.
EXT.
Time interval between the onset of two flexion movements
2
[2] Time interval between the onset of a flexion and next extension movement
80°
500 μV
0.2 s

FIG. 3. Representation of the measurements derived for quantifying the alternating movements of flexion and extension of the wrist.

Group differences in IRIs

The IRI data of two patients with Parkinson's disease and one control subject were removed because of outlying values at a number of movement frequencies. Logarithmic transformation of the data failed to correct the skewness present in the distribution of a number of the IRI measures. As analysis of variance procedures are relatively robust with regards to violations of the normality assumption if the violation is created by skewness rather than by outliers (Mardia, 1971), the statistical analyses were performed on the raw data.

For each of the five rates of movement, the mean IRIs of the patients with Parkinson's disease and the controls are shown in Table 1. Performance of self-paced repetitive alternating movements and those in synchrony with auditory stimuli are shown separately.

TABLE 1 MEAN IRIs OF THE PATIENTS WITH PARKINSON'S DISEASE AND THE CONTROLS WHEN PERFORMING SELF-PACED AND AUDITORY-PACED REPETITIVE MOVEMENTS AT THE FIVE DIFFERENT RATES

Required movement rate	*Parkinson's disease*		*Controls*	
	Self-paced	*Auditory-paced*	*Self-paced*	*Auditory-paced*
0.5 Hz (2000 ms)	1918.6 (378.4)	2034.7 (154.3)	1975.9 (101.3)	2021.4 (30.9)
1 Hz (1000 ms)	952.3 (104.3)	952.1 (71.6)	968.1 (28.7)	979.3 (25.3)
1.5 Hz (666 ms)	650.5 (125.8)	634.4 (86.1)	616.5 (44.3)	618.5 (36.8)
2 Hz (500 ms)	525.5 (116.4)	498.4 (91.0)	467.7 (28.0)	461.9 (23.9)
2.5 Hz (400 ms)	491.9 (222.3)	474.9 (243.8)	367.9 (34.6)	362.5 (35.3)

Standard deviations are given in parentheses.

A repeated measures multivariate analysis of variance (MANOVA) was carried out on the mean IRI data. Group Parkinson's disease versus control was the between subjects factor. The within subjects factors were Trigger (self-paced versus auditory-paced) and Movement Rate (0.5 Hz, 1 Hz, 1.5 Hz, 2 Hz and 2.5 Hz). The main effects of Group [F(1,57) = 1.4, $P = 0.25$] and Trigger [F(1,57) = 1.3, $P = 0.27$] and Group×Trigger interaction [F(1,57) = 0.01, $P = 0.93$] were not significant. The main effect of Movement Rate [Multivariate F(4,54) = 783.4, $P = 0.001$] and the Group×Movement Rate interaction [Multivariate F(4,54) = 3, $P = 0.03$] was significant. The two-way interaction between Trigger and Movement Rate [Multivariate F(4,54) = 2.3, $P = 0.07$] and the three-way Group×Trigger×Movement rate interaction [Multivariate F(4,54) = 0.48, $P = 0.75$] were not significant.

Further *post hoc* analyses revealed that for both self-paced and auditory-paced movements, the significant Group×Movement Rate interaction was due to the significant differences between the patients and controls at the 2 Hz (self-paced: $t = 2.9$, d.f. = 57, $P = 0.005$; auditory paced: $t = 2.4$, d.f. = 57, $P = 0.02$) and 2.5 Hz (self-paced: $t = 3.4$, d.f. = 57, $P = 0.001$; auditory-paced: $t = 2.9$, d.f. = 57, $P = 0.007$) rates of movement, but no differences at 0.5 Hz, 1 Hz and 1.5 Hz frequencies (self-paced respectively $t = 0.89$, d.f. = 57, $P = 0.38$; $t = 0.89$, d.f. = 57, $P = 0.38$; $t = 1.5$, d.f. = 57, P = 0.13; auditory-paced respectively: t = 0.52, d.f. = 57, P = 0.61; t = 1.6, d.f. = 57, P = 0.12; t = 0.99, d.f. = 57, P = 0.33). As the differences between the self-paced and auditory-paced movements and the Group × Trigger interaction were not significant, the remaining analyses will be solely based on the self-paced movements. The average personally maximal rate of performance of an 80 degrees flexion-extension movement of the wrist was 2.5 Hz (SD = 0.89) for the patients and 5.3 Hz (SD = 0.56) for the controls. The difference was statistically significant (t = 14.9, d.f. 57, P = 0.001). The mean reaction time and movement time of the patients were respectively 290.2 ms (SD = 77.4) and 328.5 ms (SD = 42.5). The corresponding values for the controls were 106.3 ms (15.5) and 101.3 ms (SD 21.4). The differences in reaction time and movement time between the groups were significant (respectively, t = 14.4, d.f. = 57, P = 0.001; t = 27.3, d.f. = 57, P = 0.001).

Effect of the severity of Parkinson's disease on IRI

For the five frequencies of the movement, the mean IRIs of the patients with mild Parkinson's disease and the subgroup with moderate or severe disease are shown in Table 2. The patients with mild Parkinson's disease showed greater accuracy in timing of repetitive alternating movements at all five movement frequencies compared with those with moderate or severe disease. To determine whether the accuracy of repetitive movements was directly proportional to the severity of Parkinson's disease, a MANOVA was performed with Severity of illness as the between subjects variable and Movement Rate as the within subjects factor. Because of the small number of cases with severe disease, the moderate and severe categories were combined. The main effect of Severity of illness was not significant at the 5% level [F(1,38) = 2.8, P = 0.10]. The main effect of Frequency of movement was significant [Multivariate F(4,35) = 157.7, P = 0.001], whereas the Severity × Movement Rate interaction was not [Multivariate F(4,35) = 0.86, P = 0.49].

TABLE 2 MEAN IRIs, REACTION TIME, MOVEMENT TIME AND MAXIMAL RATE OF 40 DEGREES FLEXION-EXTENSION MOVEMENT OF THE PATIENTS WITH MILD VERSUS MODERATE OR SEVERE PARKINSON'S DISEASE

Required movement rate	*Mild (n = 14)*	*Moderate/severe (n = 26)*
0.5 Hz (2000 ms)	1873.3 (327.7)	1943.6 (407.2)
1 Hz (1000 ms)	903.6 (96.3)	978.5 (100.6)
1.5 Hz (666 ms)	597.1 (76.9)	679.2 (138.5)
2 Hz (500 ms)	497.8 (95.5)	540.5 (125.5)
2.5 Hz (400 ms)	427.9 (102.6)	526.3 (260.9)
Reaction time	271.8 (48.7)	300.2 (88.4)
Movement time	309.9 (22.2)	338.5 (47.6)
Maximal rate of movement	2.8 (0.71)	2.3 (0.95)

Standard deviations are given in parentheses.

The mean reaction time, movement time and maximal rate of performing 80 degrees flexion-extension movements for the patients with different degrees of severity of illness are shown in Table 2. The severity of the disease had a significant effect on movement time ($t = 2.6$, d.f. = 38, $P = 0.01$) but its effect on reaction time ($t = 1.3$, d.f. = 38, $P = 0.19$) and the maximal rate of performing 80 degrees flexion-extension movements ($t = 1.8$, d.f. = 38, $P = 0.08$) failed to reach significance at the 5% level.

Effect of levodopa medication on IRI

Of the nine patients tested both in the 'off' and 'on' states, one patient was excluded because of outlying values on a number of measures. Administration of levodopa resulted in significant improvement of motor disability as evident from the KCH scores (off: mean = 51.9, SD = 16; on: mean = 17.5, SD = 6.3; $t = 7.7$, d.f. = 7, $P = 0.001$), simple reaction time (off: mean = 355.3, SD = 84.9; on: mean = 256.8, SD = 76.8; $t = 4$, d.f. = 7, $P = 0.005$) and movement time (off: mean = 371, SD = 59.9; on: mean = 197.5, SD = 64.9; $t = 6.2$, d.f. = 7, $P = 0.001$). Also, the average maximal rate of performing 80 degrees flexion-extension movements of the wrist was significantly higher ($t = 5.6$, d.f. = 7, $P = 0.001$) when the patients were tested on levodopa (mean = 3.3, SD = 0.57) than when off medication (mean = 1.6, SD = 0.70).

The mean IRIs 'on' and 'off' levodopa are shown in Table 3. As evident from Table 3, in general, accuracy of rhythmic movements was greater and the patients could perform better at higher movement frequencies in the 'on' state than when 'off' medication.

TABLE 3. MEAN IRIs OF THE PATIENTS WITH PARKINSON'S DISEASE TESTED ON AND OFF LEVODOPA MEDICATION

Required movement rate	*'Off' medication*	*'On' medication*	
0.5 Hz (2000 ms)	2075.0 (482.8)	1886.4 (65.1)	$Z = 0.84$, $P = 0.40$
1 Hz (1000 ms)	1064.0 (104.0)	965.5 (46.3)	$Z = 1.8$, $P = 0.07$
1.5 Hz (666 ms)	804.8 (194.7)	616.5 (52.6)	$Z = 2.1$, $P = 0.04$
2 Hz (500 ms)	650.0 (170.3)	444.0 (52.1)	$Z = 2.4$, $P = 0.02$
2.5 Hz (400 ms)	720.5 (411.6)	358.5 (38.3)	$Z = 2.2$, $P = 0.03$

Standard deviations are given in parentheses.

A repeated measures MANOVA was performed with medication state (on versus off) and Movement Rate as the within subjects factors. The main effects of Medication [Multivariate $F(1,7) = 9.6$, $P = 0.02$] and Movement Rate [Multivariate $F(4,4) = 41.3$, $P = 0.002$] were significant. The Medication × Movement Rate interaction was not significant at the 5% level [Multivariate $F(4,4) = 2.6$, $P = 0.19$]. However, *post hoc* examination of the differences in IRIs in the 'on' and 'off' states for each of the five individual rates of movement (Table 1) revealed that the differences were not significant for the lower rates of movement (0.5 Hz and 1 Hz), but were for the 1.5 Hz, 2 Hz and 2.5 Hz frequencies.

Application of the Wing and Kristofferson model

Test of assumptions. The theoretical model developed by Wing and Kristofferson (1973*b*) was used to break down the variability of IRIs into timekeeper and motor delay variance. The data were first checked for 'stationarity' of IRIs using the split-half method suggested by Wing and Kristofferson (1973*b*). For the controls, across the five rates of movement, the difference in mean IRIs between the first and the second half of each trial in a block was in the majority (68%) of cases zero. For the controls, the difference score was negative in 19% and positive in 13% of observations. For the patients with Parkinson's disease, the difference in mean IRIs between the first and the second set of movements was negative for most observations (42.5%), indicating an increase in mean IRI from the first to the second half. In 38.5% of observations the difference score of the patients was zero and in 19% it was positive. Considering the fact that the desired IRIs were relatively long (400–2000 ms), and that in the majority of cases the differences were negligible (less than 15 ms), a detrending transformation was not considered necessary.

The model predicts that mean lag 1 autocorrelations will be in the 0 to −0.5 range. In the present analysis we found that lag 1 auto correlations in the 0 to −0.5 range were essential for obtaining clock variances which were not larger than total IRI variance. The average lag 1 autocorrelations for the patients and control samples are presented in Table 4. As evident from the means, a proportion of the patients and controls had lag 1 autocorrelations outside the predicted range.

Therefore, for each frequency of movement, the individual data were examined to check whether lag 1 autocorrelations were in the predicted range. For each group, the number of cases who had lag 1 autocorrelation in the predicted range for each of the five rates of movement are also shown in Table 4. The percentage of cases who had lag 1 autocorrelations in the predicted range was not different in the patient and control

TABLE 4 THE MEAN LAG 1 AUTOCORRELATIONS AT EACH FREQUENCY OF MOVEMENT (A) AND THE NUMBER OF PATIENTS IN EACH GROUP WHO HAD LAG 1 AUTOCORRELATIONS IN THE 0 TO −0.5 RANGE (B)

Required movement rate	*Mean lag 1 autocorrelations*		
	Parkinson's disease (SD)	*Controls (SD)*	
(A)			
0.5 Hz	0.10 (0.28)	−0.42 (2.5)	
1 Hz	−0.01 (0.26)	−0.05 (1.6)	
1.5 Hz	−0.03 (0.30)	0.12 (0.29)	
2 Hz	0.02 (0.41)	−0.60 (2.5)	
2.5 Hz	0.08 (0.69)	0.38 (1.1)	
(B)			
0.5 Hz	12 (28.6%)	6 (30%)	$\chi^2 = 0.01$, d.f = 1, $P = 0.91$
1 Hz	22 (52.4%)	9 (54%)	$\chi^2 = 0.29$, d.f = 1, $P = 0.59$
1.5 Hz	25 (59.5%)	6 (30%)	$\chi^2 = 4.7$, d.f = 1, $P = 0.03$
2 Hz	24 (57.1%)	12 (60%)	$\chi^2 = 0.05$, d.f = 1, $P = 0.83$
2.5 Hz	21 (50%)	7 (35%)	$\chi^2 = 1.2$, d.f = 1, $P = 0.27$

groups at any rate of movement except 1.5 Hz. A larger proportion of the patients (59.5%) compared with the controls (30%) had lag 1 autocorrelations in the expected range at the 1.5 Hz rate of movement. Only one of the patients and one control had lag 1 autocorrelations in the expected range at all the five frequencies.

Group differences in variability of the central timekeeper and motor delay. At each of the five frequencies, the variability of IRIs, timekeeper and motor delay was calculated for the patients and controls who had lag 1 autocorrelations in the 0 to −0.5 range, i.e. for those subjects who met the assumption of the Wing and Kristofferson (1973*b*) model. These data are presented in Table 5. With increasing rate of movement, there was a decrease in the average variability of the IRIs, timekeeper and motor delay for both the patients with Parkinson's disease and controls. As the particular patients who met the primary prediction of the model varied across the five frequencies, and since some of the variance measures were significantly skewed, group differences were analysed using non-parametric Mann-Whitney tests on individual variance measures. The patients with Parkinson's disease had significantly greater variability of IRI, timekeeper and motor delay at all movement frequencies compared with the controls ($P < 0.001$).

TABLE 5. VARIABILITY OF IRIs, TIMEKEEPER AND MOTOR DELAY ACROSS THE FIVE FREQUENCIES OF MOVEMENT IN THE PARKINSON'S DISEASE AND CONTROL GROUPS

Required movement rate	*Parkinson's disease*			*Controls*		
	IRI	*Timekeeper variability*	*Motor*	*IRI*	*Timekeeper variability*	*Motor*
0.5 Hz (2000 ms)	26 941 (28 591)	10 243 (10 130)	8349 (12 088)	725 (979)	472 (459)	127 (136)
1 Hz (1000 ms)	3789 (2221)	2616 (1945)	587 (443)	242 (254)	163 (212)	39 (39)
1.5 Hz (666 ms)	3358 (7589)	2467 (6191)	446 (735)	139 (58)	83 (75)	28 (28)
2 Hz (500 ms)	1979 (1893)	1209 (1356)	385 (401)	155 (89)	81 (87)	37 (24)
2.5 Hz (400 ms)	1804 (1971)	1087 (1704)	358 (326)	125 (75)	78 (43)	23 (24)

Standard deviations are given in parentheses. Units are ms^2

Effect of severity of Parkinson's disease on the variability of the central timekeeper and motor delay. For the patients who had lag 1 serial autocorrelations in the 0 to −0.5 range, the effect of severity of illness on the variability of IRI, timekeeper and motor delay was examined. The relevant means, together with the results of the Mann-Whitney U tests are shown in Table 6. Although the variability of IRI, timekeeper and motor delay increased with greater severity of Parkinson's disease, except for IRI variability of movements at 1.5 Hz, differences between the mild and the moderate/severe patient groups were not significant.

Effect of levodopa medication on the variability of IRI, timekeeper and motor delay. For the self-paced repetitive movements at the 0.5 Hz, 1 Hz and 2.5 Hz frequencies, none of the patients had lag 1 autocorrelations in the expected range both 'on' and 'off' medication. For the self-paced movements at the 1.5 Hz and 2 Hz rates, respectively, three and four patients had lag 1 autocorrelations in the expected range both when tested

TABLE 6 THE MEAN IRI, TIMEKEEPER, AND MOTOR DELAY VARIABILITY FOR THE PATIENTS WITH MILD VERSUS MODERATE OR SEVERE PARKINSON'S DISEASE

	Movement rate				
	0.5 Hz	*1 Hz*	*1.5 Hz*	*2 Hz*	*2.5 Hz*
IRI variability					
Mild	9364	3556	1314	1226	1030
Moderate/severe	35 729	3951	4721	2518	2280
Mann-Whitney Z	1.5	0.30	2.1*	1.7	1.5
Timekeeper variability					
Mild	4684	2419	886	651	411
Moderate/severe	13 022	2752	3522	1607	1503
Mann-Whitney Z	1.2	0.57	1.8	1.9	1.8
Motor delay variability					
Mild	2340	568	214	287	309
Moderate/severe	11 354	599	599	456	388
Mann-Whitney Z	1.2	0.48	1.6	1.7	0.29

*$P < 0.05$

'on' and 'off' medication. At 1.5 Hz, the mean IRI, timekeeper and motor delay variability values for three patients were respectively 484.5 ms, 315.2 ms and 84.7 ms in the 'off' state and 170.3 ms, 69.2 ms and 50.5 ms following levodopa replacement therapy. For the 2 Hz movements, the average variabilities for four patients were respectively 441.1 ms, 285.3 ms and 77.9 ms 'off' medication and 73.7 ms, 38.1 ms and 17.8 ms in the 'on' state. Although the numbers are too small for statistical analysis, there is a clear reduction of the variability of all three timing parameters when 'on' levodopa compared with 'off', for both the 1.5 Hz and 2 Hz rates of movement.

DISCUSSION

The results of the study showed that patients with Parkinson's disease have problems with the accurate timing of repetitive movements. Compared with the controls the patients had longer IRIs between two successive flexion movements, with the group differences being significant at the two higher frequencies (2 Hz and 2.5 Hz). In confirmation of this, the maximal rate of performing sequential flexion-extension movements of the wrist was significantly lower in the patients than in the controls. The simple reaction and movement times also showed that the patients were significantly slower even in initiating and executing single movements.

In this study, the mean intervals produced by the patients was only significantly different from the controls at the two higher frequencies (2 Hz and 2.5 Hz), and group differences in IRIs were not significant at the lower rates of movement (0.5–1.5 Hz). Although Ivry and Keele (1989) also found a significant difference in mean IRIs between patients with Parkinson's disease and elderly controls in producing repetitive time intervals of 550 ms in duration (about 2 Hz), the mean IRIs of the patients were shorter than that of the controls, i.e. they were faster in making repetitive movements. In contrast, in the present study, the patients had significantly longer mean IRIs at the 2 Hz and 2.5 Hz rates of movement than the age-matched controls, which means that they were significantly slower. Compared with the highly trained normals studied by Wing and Kristofferson (1973*a*) who on average overestimated the inter-tap intervals by about 2 ms, both the patients and controls in the present study were much less accurate in terms of the absolute values of the IRIs producd relative to the required standard rates of movement.

Even with the auditory pacing stimuli, the observed IRIs did not completely coincide with the desired rate of movement. The IRIs for self-paced repetitive movements were not significantly different from those performed in synchrony with auditory stimuli in either the patient or control groups. This demonstrates that both patients and controls could maintain the rate of movement after cessation of the auditory stimuli which provided an external pacing of the repetitive movements during the first 30 trials. Michon (1967) examined reproduction of six time intervals in the 333–3333 ms range by tapping of a telegraph key under 'synchronization' and 'continuation' instructions, which correspond to the auditory-paced and self-paced procedures of the present study. Similar to the present results, no differences in the IRIs produced with the synchronization and continuation procedures were found.

Although not significant, increased severity of Parkinson's disease was associated with longer IRIs, i.e. slower rate of repetitive movement and less accurate timing of movements. Administration of 250 mg of levodopa/carbidopa resulted in substantial clinical improvement as evident from the significantly lower KCH ratings, shorter simple reaction and movement time and higher maximal rate of movement. Compared with when tested 'off' medication, administration of dopaminergic medication also resulted in significantly more accurate timing of repetitive sequential movements, especially at the higher (1.5 Hz, 2 Hz and 2.5 Hz) frequencies. In addition, dopaminergic medication was associated with 'normalization' of timing of repetitive movements, since the mean IRIs of the patients when tested on medication (Table 3) were not different from those of the controls (Table 1), even at higher rates of movement.

On the basis of their performance on a repetitive externally or self-paced finger-tapping task, Nakamura *et al.* (1978) categorized their sample of patients with Parkinson's disease into two groups. The first group of patients was able to produce self-paced movements without external periodic signals up to 5 Hz. The other group showed what was called a 'hastening phenomenon', i.e. an abrupt transition from the required rate of movement, usually at about 2.5 Hz, to a higher frequency usually 4–6 Hz. The hastening phenomenon noted by Nakamura *et al.* (1978) was not observed in our patient sample.

Instead, an opposite pattern was evident in the EMG records of the patients with more severe Parkinson's disease. The EMG records of these patients showed short intervals, lasting 800–1200 ms, during which the movement stopped, although tonic activity was present in the flexor and extensor muscles. At other times, the rhythmicity of movement was briefly lost by some patients and movements of different duration and amplitude were performed for a short period. Despite the presence of arrhythmicity during the performance of repetitive alternating movements, the transition to higher frequencies was never observed. This could partly be due to the fact that the subjects were required to produce movements of a fixed amplitude.

The variability of IRIs was broken down into a timekeeper variance and a motor delay variance using the Wing and Kristofferson (1973*b*) model. Compared with the controls, the patients with Parkinson's disease had significantly higher IRI, timekeeper and motor delay variance at all five rates of movement. Others (Wing *et al.*, 1984; Keele and Ivry, 1987; Ivry and Keele, 1989) have also found increased clock variance compared with controls in patients with Parkinson's disease. However, in the single case studied by Wing *et al.* (1984), motor delay variance was found to be equivalent between the affected and unaffected hand, and no differences in variability of motor implementation delay was found in the Parkinson's disease group relative to the elderly controls in Ivry and Keele's (1989) study. Motor delay variance includes an amount of variability due to kinematic factors such as changes in force. As the size of the first agonist burst is reduced in patients with Parkinson's disease (Hallett and Khoshbin, 1980), this problem in force production would be expected to be associated with greater variability of the motor implementation components.

As only one subject in each group met the criterion of lag 1 autocorrelations in the 0 to −0.5 range, for all five movement frequencies, group data could not be used to plot estimates of clock variance against the required IRI or to fit a regression line. Nevertheless, inspection of the mean clock variance at each frequency (Table 5) shows that for movements between 1 Hz and 2.5 Hz, similar to the findings of others (Wing and Kristofferson, 1973*b*; Keele *et al.*, 1985) clock variance increased with the mean IRI in both the patient and control groups. This is an expected finding, since the operation of the clock would be more variable the larger the interval being timed. However, in the Parkinson's disease group and to a lesser extent in the control group, the IRI variability and the component timekeeper and motor delay variances appear to be excessively large for repetitive movements at 0.5 Hz. As discussed below, it is possible that at such slow rates of movement, the operation of the clock is qualitatively different. Similarly, with the exception of the 0.5 Hz rate of movement, motor delay variance was relatively constant across the various IRIs for both the patients and controls. This is in line with the model and previous findings (Wing and Kristofferson, 1973*b*; Keele *et al.*, 1985).

Increased severity of Parkinson's disease was associated with greater variability of IRI, central timekeeper and motor implementation delay, although the differences between the patients with mild disease and those with moderate or severe Parkinson's disease were not significant. Administration of dopaminergic medication resulted in considerable reduction of IRI, timekeeper and motor delay variance, although the number of cases who met the basic prediction of the model was too small to allow statistical analysis.

A basic assumption of the Wing and Kristofferson (1973*b*) model is that lag 1 autocorrelations will be in the 0 to −0.5 range. Using the raw data with no preliminary 'cleaning' of the IRIs, only one of the 42 patients and one of the 20 controls met the primary prediction with regards to lag 1 autocorrelations in the 0 to −0.5 range at all five rates of movement. Across the five frequencies, this prediction was violated in 40−70% of the patients and controls. The largest proportion of the patients (60%) had lag 1 autocorrelations in the expected range at 1.5 Hz. For the controls, 2 Hz was the rate of movement at which the greatest proportion of subjects (60%) had lag 1 autocorrelations in the predicted range.

Violations of the basic assumption of the Wing and Kristofferson (1973*b*) model have been reported by others. The performance of rhythmic movements involving the swinging of pendulums by the two hands was studied by Turvey *et al.* (1989). Although the majority of lag 1 autocorrelations were negative and in the 0 to −0.5 range, 30 of the 162 correlations were positive and one was less than −0.5. Similarly, in Ivry and Keele's (1989) study the percentage of tapping blocks which showed violations of the model were found in 12.8%, 18%, 14.3% and 26% of the controls, Parkinson's disease, focal cortical lesions and cerebellar disease groups, respectively.

It should also be noted that in some of the previous studies such as those of Ivry *et al.* and Keele *et al.* (Keele *et al.*, 1987; Ivry *et al.*, 1988; Ivry and Keele, 1989) application of the Wing and Kristofferson (1973*b*) model has only been feasible because of the preliminary 'cleaning' of the raw data. For example, in Ivry *et al.*'s (1988) study of repetitive rhythmic movements in patients with lesions of the lateral or medial sections of the cerebellum, a trial was considered unsuccessful if any IRI was less than or greater than 50% of the target interval. This criterion was adopted on the basis of the assumption that any IRIs that deviated from the target interval by more than 50% could be due to either tremor or insufficient force. The use of such a criterion effectively eliminates much of the data that could have resulted in violations of the model and the very data that are characteristic of the performance of repetitive movements by patients with cerebellar disease. A similar criterion for the rejection of responses was adopted in a study with normals by Wing (1977). Furthermore, to ensure that the variability of the timekeeper was not greater than the total variability, Ivry and Keele (1989) assigned a value of zero for the motor delay whenever the lag 1 autocovariance was positive. Although it was noted that similar conclusions can be arrived at without these corrections, the assumption of zero variability for motor implementation delay is not justified, especially since variability of motor implementation, for example through lapses in attention, is most likely to have resulted in atypically long or short IRIs and hence have been the cause of lag 1 autocorrelations outside the predicted range.

Could violations of the primary assumption of the model arise from the fact that in the present study alternating flexion-extension movements of the wrist were studied? The alternation of wrist flexion with extension movements cannot be the only factor, since even movements which appear to be more discrete, such as repetitive finger tapping, also involve more than just flexion of the finger and require elevation of the finger by activating the finger-extensor muscle. A second possibility is the influence of the particular type of movement studied, which could result in violations of the predictions. Wing (1977) compared mean IRI, variance of IRIs, clock and motor delay for finger tapping alone, finger tapping involving movement of the hand about the wrist and finger tapping through raising and lowering of the forearm. While mean IRI was unrelated to the type of movement, changes in IRI variance with type of movement was found which was due not only to changes in motor delay variance but was also unexpectedly a result of changes in the variance of the timekeeper; the latter effect being significant. The lag 1 autocorrelations for the different types of movement were all in the predicted range. However, for all types of movements, trials were excluded if the subject produced intervals which differed from the standard interval of 400 ms by more than 200 ms. It is therefore not possible to determine whether different types of movement were more or less likely to violate the prediction of the model. Alternatively, could the measurement of IRIs based on flexor EMG rather than overt behavioural data have resulted in departures from the predictions? This is unlikely. Wing (1980) compared IRIs based on overt finger-tap responses with those derived from the EMG of flexors of the index finger. With average IRIs of 363 ms, the average delay from the onset of flexor EMG to the overt response was 55 ms. The intervals between overt taps had a lag 1 autocorrelation of −0.23, whereas the corresponding value for EMG derived IRIs was −0.10. It was therefore concluded that 'motor delays are defined prior to onset of muscle activity and that motor variance is not solely due to variation in the movement following onset of muscle activity' (Wing, 1980; p. 474). Therefore, departures from lag 1 autocorrelations in the 0 to −0.5 range cannot be due to the above procedural factors. A fourth possibility is that lag 1 autocorrelations outside the criterion range were obtained because the lack of 'stationarity' in the IRIs. Although a feasible problem especially for Parkinson's disease patients, calculation of mean IRIs of the first and second half of trials showed that even for the patients the differences were small and a major trend was not present.

A further assumption of the Wing and Kristofferson (1973*b*) model is that repetitive movements are performed in an open loop fashion, such that the timekeeper is not dependent on feedback from implementation of each response but operates independently of the response outcome. This raises the question of the extent to which the model is applicable to the slower rates of performing successive movements such as the 0.5 Hz included in the present study. With the IRIs set at 2000 ms, a block of trials would involve a series of discrete individual movements rather than a train of repetitive movements. The former are likely to be performed in a closed-loop fashion. This could partly explain the greater inaccuracy of subjects in both groups in producing IRIs of 2000 ms, the fact that in both groups the greatest proportion of subjects with lag 1 autocorrelations outside the expected range were for movements of 0.5 Hz, and the finding that for those who met the prediction, the variances of IRI, timekeeper and motor delay at this rate appeared over-inflated. The influence of slow rates of movement on the clock needs to be explored further.

Although the internal timekeeper and motor implementation system are assumed to be two independent processes in the model, their variances are not calculated independently, since subtraction of the motor variance from total variance is used to obtain the estimate of clock variance (Ivry *et al.*, 1988). Given this computational dependence, it is imperative to demonstrate that the two systems are functionally independent through identification of factors that would be likely to affect one but not the other component. One relevant factor may be the influence of feedback. Although, Wing and Kristofferson (1973*b*) assume that repetitive movements are performed in an open-loop mode, as noted by Ivry *et al.* (1988) feedback is likely to affect the implementation of the motor response.

In conclusion, despite its apparent conceptual appeal, the validity and utility of the model proposed by Wing and Kristofferson (1973*b*) for the study of repetitive rhythmic movements cannot be accepted as proven and require further assessment.

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QUANTITATIVE SOMATOSENSORY THERMOTEST

A KEY METHOD FOR FUNCTIONAL EVALUATION OF SMALL CALIBRE AFFERENT CHANNELS

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SUMMARY

The quantitative somatosensory thermotest (QST) assesses the function of afferent channels concerned with sensory submodalities served by small calibre fibres. Measured ramps of ascending or descending temperature are applied to the skin through a Peltier contact thermode, and detection thresholds are recorded as the subject signals the onset of a particular sensation.

The present study describes underlying principles, methodological aspects and normal reference values for the QST. In patients, measurement of thresholds for cold sensation, warm sensation, cold-induced pain and heat-induced pain, applied to 465 individuals, yielded 13 abnormal patterns segregated into three main groups: (i) thermal (cold or warm) hypoaesthesia; (ii) thermal hyperalgesia (abnormally reduced threshold for cold and/or heat induced pain); (iii) thermal hypoaesthesia combined with thermal hyperalgesia.

Critical analysis of these results yielded a number of observations of general relevance: (i) thermal specific (warm or cold) hypoaesthesia and thermal (heat or cold) hyperalgesia may occur in the absence of hypoaesthesia for tactile submodalities served by large calibre afferents; (ii) cold hypoaesthesia and warm hypoaesthesia may dissociate from each other; (iii) thermal pain hyperalgesias may occur in the absence of hypoaesthesias for specific cold or warm sensations; (iv) cold hyperalgesia and heat hyperalgesia may dissociate from each other.

Thus, a negative routine sensory examination and unimpaired sensory nerve action potentials do not exclude possible somatosensory dysfunction. Furthermore, while most methods of sensory testing only document normality or deficit, the QST permits additional documentation of hyperalgesia, a positive sensory phenomenon that implies unusual pathophysiologies such as sensitization of receptors, central hyperexcitability, disinhibition or, possibly, ectopic nerve impulse discharge.

This psychophysical test does not specify the level within afferent channels, between skin and brain-mind, where the abnormality resides. It is recommended that the QST for all four thermal specific and thermal pain functions be incorporated in routine neurological assessment.

INTRODUCTION

Conventional clinical and laboratory investigation of patients with neurological sensory disorders falls short at two significant levels: (i) evaluation of the status of small calibre afferent systems and (ii) determination of the neurophysiological basis for positive sensory phenomena (Ochoa, 1987). The advent of quantitative sensory tests has made it possible to apply controlled and quantifiable natural thermal stimuli to evoke specific sensations which are measurable psychophysically. This opens an opportunity to explore order and disorder in somatosensory channels served by small calibre fibres in a non-invasive, yet rigorous, fashion.

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A number of methods have been promoted over the last two decades to fulfill this aim (Marks and Stevens, 1972; Dyck *et al.*, 1978; Bertelsmann *et al.*, 1985; Jamal *et al.*, 1985; Fowler *et al.*, 1987). The Marstock method (Fruhstorfer *et al.*, 1976) permits measurement of both warm and cold specific functions and, also, of pain induced by noxious high and low temperature stimuli. This multiplies the overall sensitivity of the method by allowing detection not only of deficit of sensory function but also of its 'exaggeration' in the form of heat or cold hyperalgesia, pervasive phenomena which are often missed in clinical routine.

Here we report our experience in the use of the quantitative sensory thermotest (QST), performed by the Marstock method, interpreted in light of normal control values and with the advantage of customized clinical, electrophysiological, thermographic, autonomic and (sometimes) neuropathological evaluation of several hundred patients with somatosensory disorders. We emphasize aspects of instrumentation, methodology, indications and interpretation of results. We also refer to specific sensory syndromes which can be detected and properly defined through the application of the QST, in the context of multidisciplinary assessment.

MATERIALS AND METHODS

Subjects

Informed consent was obtained from all normal subjects and patients according to the Declaration of Helsinki.

Normal subjects. Sixty-one volunteers without history of neurological disease, 24 males and 37 females (age range 17–72 yrs, mean 38.8 yrs), served as normal controls. Three areas of skin were tested on each person: one thenar eminence, one hypothenar eminence and one tarsal region.

Patients. Between January 1987 and December 1989, the QST was performed on 465 patients referred to the Neuromuscular Unit, Good Samaritan Hospital and Medical Center, with somatosensory dysfunction, mostly related to disorders of the peripheral nervous system. Here we present results of the test on 402 of those subjects in whom the test was carried out in at least one thenar eminence, one hypothenar eminence or one tarsal region. The group included 180 men and 222 women (age range 12–90 yrs, mean 49 yrs).

Quantitative thermal stimulator

The thermostimulator operates by the Peltier principle. Passing an electrical current through two dissimilar semiconductors displaces heat in the direction of the current. If a good heat conductor, such as a metallic plate, is juxtaposed to one side of the semiconductor system, it will be heated or cooled depending on the direction of the current. The plate increases in temperature when the current flows towards it and decreases when the current flows away. Intensity of the current determines the rate of change in temperature. The opposite side of the system is buffered by water at 25°C, which acts as a heat sink or heat source depending on the direction of current. Current direction can be reversed at any time by two switches, one operated by the subject who is instructed to signal onset of a given sensation, and the other by the examiner to electively initiate or reverse the stimulus ramp. The temperature at the surface of the stimulator probe is measured through a built-in thermocouple made of dissimilar wires (copper and constantin) whose voltage difference varies in response to change in temperature. Two rectangular probe sizes may be used for cutaneous stimulation. The larger has a surface of 12.5 cm^2 and is useful everywhere on the skin except for small or curved areas, such as fingers. In these regions a smaller probe (3.8 cm^2) is used. A d.c. power supplier provides current with a maximum output of 10 V and 9 A. The apparatus displays digitally the current and the temperature measured by the thermocouple. The ramps of applied temperature are graphed through a calibrated pen recorder connected to the Marstock apparatus. The turning points reflect the signalled subjective thresholds expressed in degrees centigrade.

General recording arrangements

The test is performed in a draft free, 25 °C, silent room suitable for psychophysical studies. The subject relaxes on a recliner, without visual access to the display screen or the silent graphic plotter. Subjects are instructed to press the reversal switch as soon as a specified submodality of thermal sensation, evoked by the stimulator, is first perceived. Pressing the switch immediately reverses the direction of the current, driving the stimulator to baseline temperature.

The recommended machine settings are as follows:

Current. For cold and warm sensation thresholds a current of 25% of the maximal output of the apparatus, equivalent to 2.25 Å is used. For cold pain, the current is fixed initially at 40% (3.6 Å) and is gradually increased up to 75% (5.4 Å). For heat pain, the current is fixed at 40% (3.6 Å). These values determine a rate of change in temperature of approximately 2 °C/s for warm and cold sensory thresholds, and 4 °C/s for thermal pain thresholds. The relation between current and rate of temperature change is complex. The rate of temperature change measured at the skin-thermode junction will depend on the thermal mass of the area where the thermode has been attached. The thermal mass will depend on ambient temperature, initial skin temperature and blood flow. Obviously, temperature measured by the built-in thermocouple will not reflect the temperature gradient within the depth of the volume of the limb. Nevertheless, it is clear that the apparatus delivers thermal energy, which, depending on amount, evokes specific sensations of warmth or of heat pain.

Baseline temperature. In order to minimize the variability of threshold levels between individuals, the contact probe is applied at a standard baseline temperature of 32 °C. This temperature is within the 'neutral zone of adapting temperature' (31 °C–36 °C) at which any thermal sensation induced by application of the probe rapidly vanishes by adaptation (Darian-Smith, 1984).

Setting the highest and lowest temperature limits. The high temperature limit is set at 50 °C and the low at 5 °C, in order to prevent thermal injury and to protect the Peltier instrument. When these temperatures are reached, the direction of current is automatically reversed, thus driving the stimulator to baseline.

Calibration of the pen recorder. The 32 °C level used as baseline temperature is set just above midway in the 26.5 cm wide paper strip. Pen displacement is set for 6 mm/°C. Paper speed is set at 1 cm/min.

The following stimuli are presented sequentially: decreasing temperature to cold sensation, increasing temperature to warm sensation, decreasing temperature to cold pain threshold and increasing temperature to heat pain threshold. For determination of cold and warm sensory thresholds the subject is instructed to press the switch as soon as a change of temperature is detected. Normally the first sensation experienced is appropriately warm or cold. For cold pain and heat pain thresholds the subject is instructed to signal the instant of first pain, disregarding intervening warm or cold sensations. Subjects are asked to describe the subjective quality of the sensation being signalled in view of possible paradoxical responses. Each submodality is tested three to six times. The test takes approximately 10 min for each site evaluated. The average of the values signalled by the subject is considered the threshold for each sensation. Thermal specific cold and warm sensations are tested before thermal pains because relative extremes of temperature stimulation may elicit lingering after-sensations. In the record obtained, each peak represents the value signalled by the patient in response to each stimulus ramp presented. This allows for convenient visual analysis of the profile.

RESULTS

Normal subjects

The quantitative thermotest profile typically obtained in normal subjects is shown in Fig. 1A. The mean normal thresholds for cold, warm, cold pain and heat pain sensations are presented in Table 1. A linear correlation between age and warm sensation threshold was found only for the tarsal region. Several subjects did not possess cold pain sensation at 5 °C: three on the hypothenar eminence and eight on the tarsal region. For these subjects a value of 5 °C was assumed for cold pain threshold when calculating mean and standard deviation. There were also subjects who did not express heat pain sensation at 50 °C: two on the hypothenar eminence and two on the tarsal region. For these subjects a value

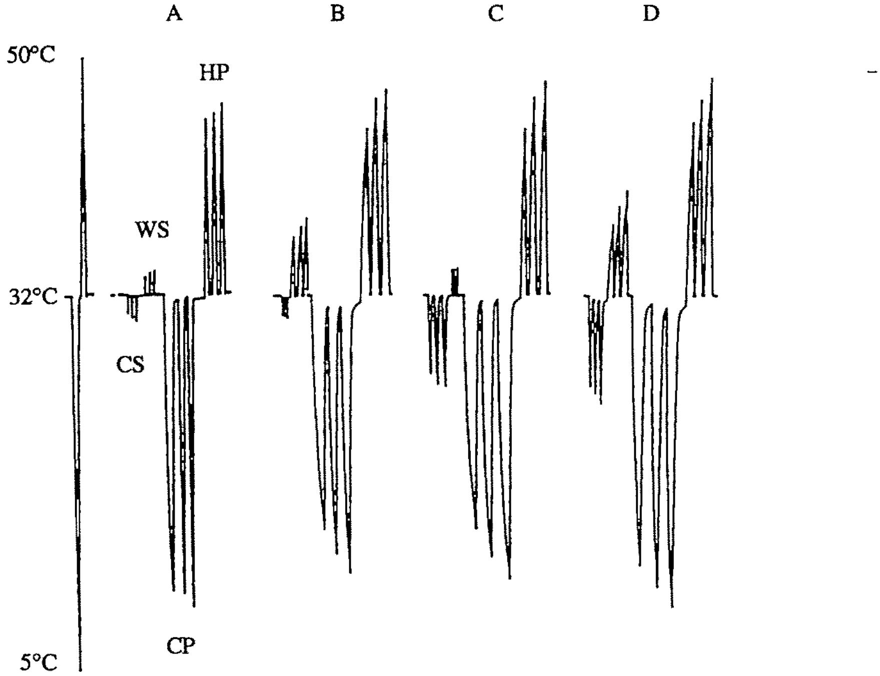

FIG. 1. Thermal hypoaesthesia. A, normal pattern; B, pure warm hypoaesthesia (75 patients); C, pure cold hypoaesthesia (173 patients); D, combined cold and warm hypoaesthesia (141 patients). CS = cold sensation; WS = warm sensation; CP = cold pain; HP = heat pain. Each sensation was tested with three stimuli presentations in this and all subsequent figures.

TABLE 1 MEAN THRESHOLDS FOR COLD, WARM AND THERMAL PAIN SENSATIONS IN NORMAL SUBJECTS

	Cold sensation	*Warm sensation*	*Cold pain*	*Heat pain*
Thenar eminence	30.6 (0 4)	33 5 (1.2)	12.3 (4 4)	44 6 (1 9)
Hypothenar eminence	30.0 (0.9)	33.7 (0 7)	9 0 (8.2)	45.7 (3.3)
Tarsal region	29 5 (1 9)	36.4 (3.3)*	10 1 (6.6)	43 9 (2 6)

*There is a linear correlation between age and mean threshold for warm sensation Slope = 0 08; r = 0 345, ($P < 0\ 01$). SDs are given in brackets

of 50°C was assumed for heat pain threshold when calculating mean and standard deviation.

Patients

The 402 patients were tested on different body sites depending upon the clinical picture: 186 patients were tested on the right thenar eminence and 245 on the left, 92 on the right hypothenar eminence and 94 on the left, and 257 on the right tarsal region and 267 on the left.

For cold and warm sensation, abnormalities relate only to *elevation* of thresholds, since normal variability within a narrow range of temperature around 32 °C does not allow reliable evaluation of hypothetically *reduced* thresholds. Criteria for warm hypoaesthesia and cold hypoaesthesia were defined as thresholds greater than the mean plus two standard deviations from the values obtained in normal volunteers. Therefore warm hypoaesthesia was diagnosed for thresholds equal to or above 36.1 °C on the thenar eminence and 35.2 °C on the hypothenar eminence. For the tarsal region, the mean threshold for warm sensation in control subjects was plotted against age. Warm hypoaesthesia was diagnosed when the mean threshold for warmth fell outside the 95% confidence limits of the regression line for age. Cold specific hypoaesthesia was diagnosed for mean thresholds equal to or below 29.8 °C on the thenar eminence, 28.2 °C on the hypothenar eminence and 25.6 °C on the tarsal region.

For cold pain and heat pain a threshold lower than the normal mean minus two standard deviations was considered cold pain or heat pain hyperalgesia. Cold pain hyperalgesia was diagnosed when the mean threshold for cold pain was at temperatures higher than 21.1 °C on the thenar eminence, 25.5 °C on the hypothenar eminence and 23.5 °C on the tarsal region. Heat pain hyperalgesia was diagnosed when the mean threshold for heat pain was below 40.8 °C, 39.2 °C and 38.7 °C at those three sites, respectively.

Cold pain and heat pain hypoalgesia were not considered because several normal subjects expressed no cold pain or heat pain sensation within the range of thermal stimulation applied. Nevertheless, for a number of patients there was a striking increase in the threshold for cold and/or heat pain on the affected part of the body relative to the asymptomatic areas tested, indicating the presence of relative cold or heat hypoalgesia. Detection of cold or heat hypoalgesia through comparing heat pain and cold pain thresholds between homologous or different parts of the body would require statistical analysis of thresholds for heat and cold pain at different sites of the body in a large number of normal subjects. This is not available.

On the basis of these criteria the test was considered normal on all sites tested in 79 patients (31 males and 48 females, age range 12–78 yrs; mean 41.8 yrs).

In 323 patients the test was considered abnormal on at least one site. Patients often exhibited different abnormal patterns at different sites tested.

Patterns of abnormality

A spectrum of abnormal quantitative thermotest profiles emerged from the examination of patients. These consisted of combinations of cold or warm hypoaesthesia, and of cold or heat hyperalgesia.

Thirteen distinct combined profiles of abnormal thermotest emerged as real occurrences out of the 36 possible theoretical combinations. They are grouped in three major categories: (ii) pure hypoaesthesia; (ii) pure hyperalgesia; (iii) hypoaesthesia associated with hyperalgesia.

Pure hypoaesthesia

Pure warm hypoaesthesia. This pattern (Fig. 1B), was observed in 75 patients, 46 males and 29 females, aged 22–84 yrs (mean 50.5 yrs) (*see* Table 2).

In 39 patients, this pattern was present on the *tarsal* region, unilaterally in 30 and

TABLE 2 DISTRIBUTION OF PATIENTS ACCORDING TO ABNORMAL PATTERN AND DIAGNOSIS PURE HYPOAESTHESIA

	Abnormal patterns		
Diagnosis	*Pure warm hypoaesthesia*	*Pure cold hypoaesthesia*	*Warm and cold hypoaesthesia*
Polyneuropathy	34	64	78
Mononeuropathy muliplex	5	4	2
Mononeuropathy	15	22	20
Radiculopathy	4	17	6
Reflex sympathetic dystrophy	7	24	14
Brachial plexus lesions	2	5	4
Motor neuron disease	–	8	2
CNS lesions	2	1	2
Psychogenic	6	28	13
Total	75	173	141

bilaterally in nine. For the 48 tarsal regions displaying this pattern the mean thresholds (±SD) were: warm sensation 45.1°C (±1.69); cold sensation 27.5°C (±1.53); cold pain 12.8°C (±5.75) and heat pain 47.5°C (±1.37).

In 17 patients, pure warm hypoaesthesia was present unilaterally on the *thenar* region. Mean threshold for the blunted warm sensation on the affected thenar regions was 38.6°C (±2.59). On the 17 thenar regions the mean threshold for cold sensation was 30.4°C (±0.41), for cold pain it was 10.2°C (±6.08) and for heat pain 46.5°C (±2.27).

Pure warm hypoaesthesia was found on the *hypothenar* region in 26 patients, unilaterally in 22 and bilaterally in four. The mean threshold for warm sensation on the affected hypothenar eminences was 36.6°C (±2.05). For cold sensation the mean threshold was 29.3°C (±0.71), for cold pain 10.2°C (±6.36) and for heat pain 48.0°C (±2.2).

Pure cold hypoaesthesia. Pure cold hypoaesthesia (Fig. 1C) was present in 173 patients, 79 males and 94 females, aged 14–90 yrs (mean 52.3 yrs) (*see* Table 2).

In 72 patients the pattern was present in the *tarsal* region: 62 in one foot and 10 in both. The mean threshold for cold sensation on the affected tarsal regions was 19.7°C (±5.33), for warm sensation it was 40.3°C (±2.06), for cold pain 7.7°C (±4.46) and for heat pain 44.9°C (±2.5).

Pure cold hypoaesthesia was found on the *thenar* region in 116 patients: 88 in one hand and 28 in both. The mean threshold (±SD) for cold sensation on the 144 affected thenar eminences was 28.5°C (±2.11). On the same thenar eminences the mean threshold for warm sensation was 34.3°C (±0.98), for cold pain it was 9.1°C (±4.5) and for heat pain 46.4°C (±2.62).

Pure cold hypoaesthesia was found on the *hypothenar* eminence in 11 patients, seven in one hand and four in both. The mean threshold for cold sensation on the 15 hypothenar eminences was 26.2°C (±2.11), for warm sensation it was 33.6°C (±1.0), for cold pain 10.0°C (±4.6) and for heat pain 47.3°C (±2.63).

Cold plus warm hypoaesthesia. Elevation of threshold for both cold and warm sensation (Fig. 1D) was seen in 141 patients, 69 males and 72 females, aged 14–88 yrs (mean 56.1 yrs) (*see* Table 2).

In 92 patients the pattern was present on the tarsal region: 61 in one foot and 31 bilaterally. The mean threshold for cold sensation on the 123 tarsal regions was 11.7°C (±7.57). For warm sensation the mean threshold was 46.6°C (±2.1). The mean threshold for cold pain was 5.9°C (±2.38) and for heat pain it was 48.1°C (±1.72).

Cold and warm hypoaesthesia was found on the *thenar* eminence in 47 patients: 36 in one hand and 11 in both. The mean threshold for cold sensation on the 58 thenar eminences was 22.7°C (±6.8). For warm sensation the mean threshold was 40.9°C (±4.48). On the same thenar eminences the mean threshold for cold pain was 8.5°C (±4.59) and for heat pain it was 47.1°C (±2.48).

Cold and warm hypoaesthesia was present on the *hypothenar* eminence in 30 patients: 19 in one hand and 11 in both. The mean threshold for cold sensation on the 40 hypothenar eminences was 24.0°C (±5.14) and for warm sensation it was 40.0°C (±4.74). For cold pain the mean threshold was 9.1°C (±5.46) and for heat pain 48.1°C (±2.1).

Pure hyperalgesia

In this group of abnormal patterns there was a lowered threshold for cold pain and/or heat pain, with normal thresholds for cold and warm specific sensations.

Pure cold pain hyperalgesia. In this pattern there is isolated reduction of the threshold for cold pain (Fig. 2B). It is conceivable that associated cold specific hypoaesthesia might

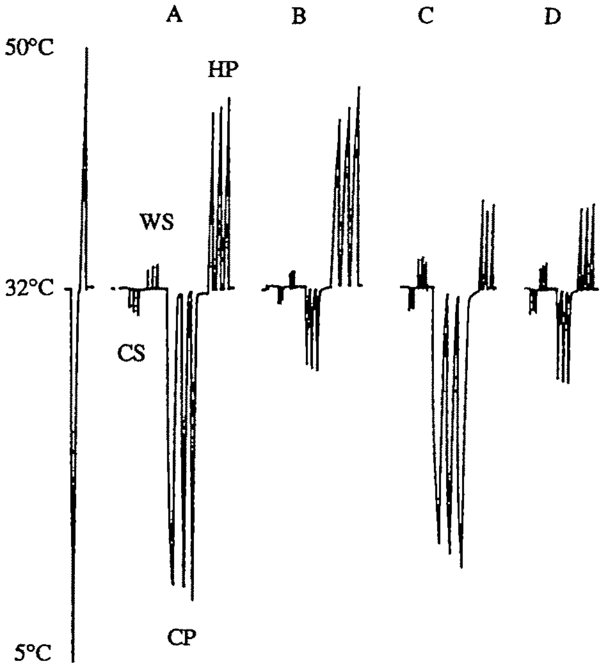

FIG. 2 Pure cold pain and/or heat pain hyperalgesia. A, normal pattern; B, pure cold pain hyperalgesia (30 patients); C, pure heat hyperalgesia (26 patients); D, combined cold pain and heat pain hyperalgesia (five patients). CS = cold sensation; WS = warm sensation; CP = cold pain; HP = heat pain

be masked if the cold pain hyperalgesia gave a clue to temperature change. However, many of these patients also had paradoxical heat sensation in response to low temperature stimulation, ruling out that possible artefact at least in that group.

The pattern was observed in 30 patients, 13 men and 17 females, aged 13–74 yrs (mean 41.8 yrs) (*see* Table 3).

TABLE 3 DISTRIBUTION OF PATIENTS ACCORDING TO ABNORMAL PATTERN AND DIAGNOSIS PURE HYPERALGESIA

	Abnormal patterns		
Diagnosis	*Pure cold pain hyperalgesia*	*Pure heat pain hyperalgesia*	*Cold and heat pain hyperalgesia*
Polyneuropathy	5	12	–
Mononeuropathy	3	–	–
Radiculopathy	5	–	–
Motor neuron disease	4	–	–
Reflex sympathetic dystrophy	6	6	3
CNS lesions	2	–	–
Psychogenic	5	8	2
Total	30	26	5

It was found on the *tarsal* region in 26 patients, 23 in one foot and three in both. The mean threshold for cold pain on the 29 tarsal regions was 26.3°C (±1.90). The mean threshold for cold sensation on the same regions was 28.8°C (±1.27), for warm sensation it was 37.3°C (±2.91) and for heat pain it was 43.5°C (±2.51).

Pure cold pain hyperalgesia was found on the *thenar* eminence in six patients, unilaterally in all of them. The mean threshold for cold pain on the six thenar eminences was 24.3°C (±3.11).

Pure cold pain hyperalgesia was found on the hypothenar eminence in only one patient.

Pure heat hyperalgesia. In this abnormal pattern there is isolated reduction of the threshold for heat pain (Fig. 2c). It was observed in 26 patients, eight males and 18 females, aged 16–90 yrs (mean 43.8 yrs) (*see* Table 3).

The pattern was found on one *tarsal* region in three patients. The mean threshold for heat on the three tasal regions was 37.7°C. The mean threshold for cold sensation was 29.3°C, for warm sensation it was 36.2°C and for cold pain 17.1°C.

The pattern was found on the *thenar* eminence in 20 patients, 15 in one hand and five in both. The mean threshold for heat pain on the 25 affected thenar eminences was 39.2°C (±1.15). The mean threshold for cold sensation was 30.7°C (±0.45), for warm sensation 33.2°C (±1.23) and for cold pain 12.5°C (±5.24).

Pure heat hyperalgesia was present on the *hypothenar* eminence in four patients: on one hand in three and on both in one. The mean threshold for heat pain on the five hypothenar eminences was 37.6°C (±1.19); for cold sensation it was 29.9°C (±0.64) and for cold pain 21.6°C (±2.4).

Cold pain plus heat pain hyperalgesia. In this pattern there are lowered thresholds for cold pain and heat pain and normal thresholds for cold and warm sensation (Fig. 2D). It is possible that warm and/or cold hypoaesthesia could be present, but masked, if the patient utilized thermal pain as a cue to discriminate thermal sensation. The pattern was observed in five patients, two men and three women, aged 29–64 yrs (mean 42.6 yrs) (*see* Table 3).

This abnormal pattern was found on one *tarsal* region in two patients whose mean thresholds were: cold pain 27.3 °C, heat pain 38.5 °C, cold sensation 27.8 °C and warm sensation 33.4 °C.

The pattern was found on one *thenar* eminence in two patients whose mean threshold for cold pain was 26.4 °C and for heat pain 36.4 °C.

Heat pain plus cold pain hyperalgesia was found on one *hypothenar* region in only one patient.

Thermal specific hypoaesthesia associated with cold and/or heat pain hyperalgesia

In this group of abnormal patterns there is cold and/or warm hypoaesthesia associated with cold pain and/or heat pain hyperalgesia.

Warm hypoaesthesia plus cold pain hyperalgesia. In this pattern there is an elevated threshold for warm sensation and a lowered threshold for cold pain (Fig. 3B). It was observed in six patients, three men and three women, aged 31–77 yrs (mean 54.5 yrs) (*see* Table 4).

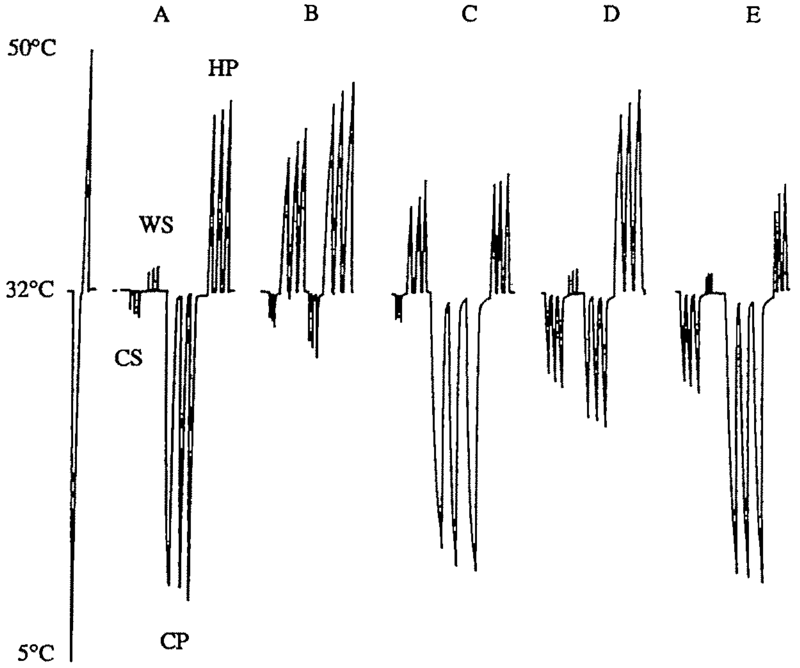

FIG. 3 Thermal hypoaesthesia combined with thermal pain hyperalgesia. A, normal pattern; B, warm hypoaesthesia associated with cold pain hyperalgesia (six patients); C, warm hypoaesthesia associated with heat pain hyperalgesia (one patient); D, cold hypoaesthesia associated with cold pain hyperalgesia (four patients); E, cold hypoaesthesia associated with heat pain hyperalgesia (17 patients). CS = cold sensation; WS = warm sensation; CP = cold pain; HP = heat pain.

The pattern was present on one *tarsel* region in four patients. The mean threshold

TABLE 4 DISTRIBUTION OF PATIENTS ACCORDING TO ABNORMAL PATTERN AND DIAGNOSIS HYPOAESTHESIA ASSOCIATED WITH HYPERALGESIA

	Abnormal patterns						
Diagnosis	*Warm hypo Cold pain hyper*	*Warm hypo. Heat pain hyper.*	*Cold hypo Cold pain hyper.*	*Cold hypo. Heat pain hyper.*	*Cold hypo. Heat pain hyper Cold pain hyper.*	*Cold hypo. Warm hypo. hyper hyper.*	*Cold hypo Warm hypo Cold pain hyper. Heat pain hyper.*
Polyneuropathy	3	–	–	5	2	–	1
Mononeuropathy multiplex	1	–	–	1	–	–	–
Mononeuropathy	1	–	–	–	1	1	–
Radiculopathy	–	–	–	1	1	–	–
Reflex sympathetic dystrophy	1	–	1	1	–	–	–
CNS lesions	–	–	1	1	–	–	–
Psychogenic	–	–	2	8	1	–	–
Total	6	1	4	17	5	1	1

for warm sensation was 44.5°C (±1.71), for cold pain 28.3°C (±2.01), for cold sensation 29.3°C (±1.39) and for heat pain 46°C (±1.87).

The pattern was found on the *thenar* eminence in only one patient.

Warm hypoaesthesia with cold hyperalgesia was found on the *hypothenar* region in only one patient.

Warm hypoaesthesia plus heat pain hyperalgesia. In this pattern there is elevation of the threshold for warm sensation with a lowered threshold for heat pain, but normal cold sensation and cold pain (Fig. 3c).

This abnormal pattern was found in only one patient, on the thenar eminence (*see* Table 4).

Cold hypoaesthesia plus cold pain hyperalgesia. Elevation of the threshold for cold sensation associated with lower threshold for cold pain and a normal threshold for warmth and heat pain (Fig. 3D) was found in four patients, three men and one woman, aged 23–66 yrs (mean 37 yrs).

It was found on the *tarsal* region in one patient, and on the *thenar* eminence in three patients (*see* Table 4). On the affected thenar eminences the mean threshold for cold sensation was 29.4°C (±0.41) and for heat pain 22.1°C (±1.33).

Cold hypoaesthesia plus heat pain hyperalgesia. Elevation of the threshold for cold sensation associated with lowered threshold for heat pain (Fig. 3E) was found in 17 patients, eight men and nine women, aged 30–70 yrs (mean 43.2 yrs) (*see* Table 4).

The pattern was found on one tarsal region in three patients. The mean threshold for cold sensation on the three tarsal regions was 21.4°C and for heat pain 37.4°C.

Cold hypoaesthesia with heat hyperalgesia was found in one *thenar* eminence in 13 patients. The mean threshold for cold sensation was 27.1°C (±3.93) and for heat pain 38.4°C (±2.19). For warmth the mean threshold was 33.4°C (±1.37) and for cold pain it was 13.6°C (±5.16).

Cold specific hypoaesthesia associated with heat pain hyperalgesia was found on the *hypothenar* eminence in only one patient.

Cold hypoaesthesia plus cold pain and heat pain hyperalgesia. In this pattern there is an elevated threshold for cold sensation and a lowered threshold for cold pain and heat pain (Fig. 4B). It was detected in five patients, one man and four women, aged 32–78 yrs (mean 53.4 yrs) (*see* Table 4). The pattern was present on one thenar eminence in four patients. The mean threshold for cold sensation on the four thenar eminences was 28.1 °C (±2.28). For cold pain the mean threshold was 24.8 °C (±1.58), for heat pain 38.0°C (±1.17) and for warm sensation 34.6°C (±0.86).

The pattern was found on one *hypothenar* eminence in two patients.

Cold plus warm hypoaesthesia and cold pain hyperalgesia. Hypoaesthesia for cold and warm sensation associated with lower thresholds for cold pain (Fig. 4C) was observed in only one patient (*see* Table 4).

Cold and warm hypoaesthesia plus cold pain and heat pain hyperalgesia. In this pattern there is an elevated threshold for cold and warm sensation and a reduced threshold for cold pain and heat pain (Fig. 4D). It was observed in only one patient (*see* Table 4).

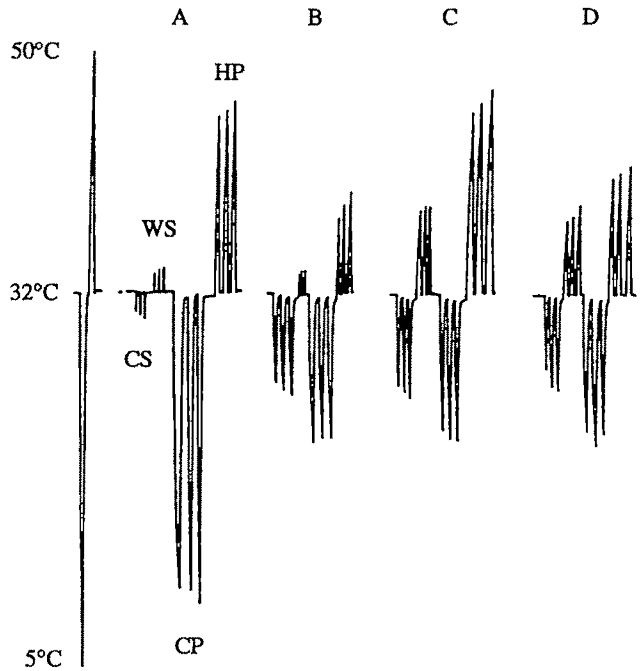

FIG. 4. Thermal hypoaesthesia combined with thermal pain hyperalgesia (continuation of Fig. 3). A, normal pattern; B, cold hypoaesthesia associated with cold and heat pain hyperalgesia (five patients); C, cold and warm hypoaesthesia associated with cold pain hyperalgesia (one patient); D, cold and warm hypoaesthesia associated with cold and heat pain hyperalgesia (one patient) CS = cold sensation; WS = warm sensation; CP = cold pain; HP = heat pain.

DISCUSSION

General significance

A substantial number of original studies have been published on the use of the QST in human somatosensory clinics and research. The present work complements available knowledge by contributing standardized normal control values, both for thermal specific and thermal pain thresholds on the human hand and foot, and in describing a range of abnormal patterns encountered during the systematic evaluation of large numbers of patients with sensory symptoms, mostly related to polyneuropathy and nerve trauma. The results and conclusions are authenticated by correlation with other criteria derived from multidisciplinary clinical, conventional electrophysiological, thermographic and histopathological data, all collected and analysed by the authors using uniform criteria.

Several points of overall significance are worth highlighting before discussing the present results in detail. (i) The test explores quantitatively the function of small calibre afferent channels, thus contributing a missing cornerstone in clinical evaluation of somatosensory status, which conventional electrophysiology covers only for large calibre channels through measurement of sensory nerve action potentials and somatosensory evoked potentials. (ii) The test provides key formation about four separate somatosensory functions: warm sensation, cold sensation, heat pain, and cold pain, each subserved by a physiologically specific apparatus wired at primary sensory neuron level by small calibre myelinated or unmyelinated fibres. Since pathological states may affect differentially the structure and physiology of those neuronal systems, their corresponding somatosensory functions may break down independently. Therefore, it would not be legitimate to draw conclusions about the status of small calibre afferents when testing purely for thermal specific warm or cold sensory functions. Further, the status of channels concerned with heat and cold pain must be explicitly tested since heat pain is not hyperbole of warm sensation and cold pain is equally unrelated to cold sensation. (iii) The test explores abnormal deviation of small calibre afferent function not only in the direction of deficit but also in the direction of irritative positive phenomena, specifically, hyperalgesia. This contributes an exclusive documentation of dysfunction that is not quantifiable by conventional methods, electrophysiological or otherwise (Ochoa, 1987). Such a feature is critical in the study of neurological painful syndromes where heat and cold hyperalgesia may exist in the absence of derangement of warm or cold specific sensory function.

It would be realized that the test explores the status of somatosensory afferents all the way between cutaneous receptor and brain/mind, without providing clues as to the precise locus of dysfunction along the channels. This limitation may be circumvented through an integrated analysis of other clinical and laboratory data. Besides, this feature may constitute an advantage in that the characteristics of a QST profile and its degree of consistency over time might support or reject abnormal psychogenic contribution.

Given these general properties, the QST emerges as indispensable for a refined evaluation of human somatosensory function in the clinic and in research.

Afferent systems subserving thermal specific and thermal pain sensations

Cold sensation. The neural apparatus known to underlie the sensation of cold in man is served at the primary afferent level by small calibre myelinated fibres. Basic studies support the concept that cold sensation is evoked by activity in primary afferent units subserved by A δ myelinated fibres. This is based on direct stimulus/response data gathered through recording electrophysiologically identified single afferents in animals (Darian-Smith *et al.*, 1973; Georgopoulos, 1976) and in man (Adriaensen *et al.*, 1983). Human psychophysical studies provide supplementary evidence through the observation of the behaviour of cold sensation during differential nerve fibre blocks (MacKenzie *et al.*, 1975; Fruhstorfer, 1984; Yarnitsky and Ochoa, 1990*b*) or through measurement of reaction times for evoked cold sensation (Fruhstorfer, 1976). Recently, indirect measurement of conduction velocity of afferent input related to cold sensation (Fowler *et al.*, 1988) has further endorsed the notion that A δ fibres convey the primary neural message that is cognitively decoded as cold sensation. More recently, the same conclusion was reached during human experimental studies based on a different methodology (Yarnitsky and Ochoa, 1991*b*). Direct correlations between low temperature stimulus, afferent neural message and subjective experience of cold sensation in humans continue to be awaited: a major experimental challenge.

Warm sensation. The neural apparatus that carries the afferent input triggered by non-noxious elevation of temperature, evoking the sensation of warmth, uses unmyelinated fibres at the primary sensory neuron level. This concept is based on direct stimulus-response behaviour of physiologically identified single warm specific afferents in animals (Darian-Smith *et al.*, 1979; Duclaux and Kenshalo, 1980) and in man (Konietzny and Hensel, 1975; Hallin *et al.*, 1982). Human psychophysical studies on warm sensation during differential nerve fibre blocks further support the concept (Lewis *et al.*, 1931; Gasser, 1935; Sinclair and Hinshaw, 1950; Torebjörk and Hallin, 1973; MacKenzie *et al.*, 1975; Fruhstorfer, 1984; Yarnitsky and Ochoa, 1991*a*), as do reaction time measurements (Fruhstorfer, 1976; Fowler *et al.*, 1988; Yarnitsky and Ochoa, 1991*b*).

While direct evidence on correlations between elevated temperature stimulus, afferent neural message and subjective sensory experience of warmth in humans (also a major experimental challenge) is pending, it is generally accepted that indirect correlations between stimulus/neural response in animals and stimulus/warm sensory experience in humans ratify C-unmyelinated fibres as mediators of this sensation.

Confirmatory evidence that A δ myelinated fibres subserve cold sense while unmyelinated fibres subserve warm sense ought to accrue from strategic clinicopathological correlations in patients with selective loss of either population of nerve fibres. However, in reviewing publications on the subject, one finds that cold and warm sensations are usually not described as separate submodalities. Terms such as 'temperature discrimination' used to describe the profile in a patient with selective loss of small myelinated fibres (Low *et al.*, 1978), or 'temperature sensation' in another such case (Donaghy *et al.*, 1987), or 'insensitivity to painful and thermal stimuli' in a patient with absence or agenesis of unmyelinated fibres and insensitivity to pain (Bischoff, 1979), fail to establish the anticipated correlation.

Heat pain. The neural apparatus that carries afferent input induced by noxious heat, evoking the sensation of burning heat pain, is known to be served by unmyelinated fibres at the primary sensory neuron level. This concept is based on abundant stimulus-response data directly obtained through recording physiologically identified single unmyelinated afferents in animals (Iggo and Ogawa, 1971; Dubner and Beitel, 1976; Georgopoulos, 1976) and in man (Torebjörk, 1974; Van Hees and Gybels, 1981; Hallin *et al.*, 1982; Torebjörk, 1985; Yarnitsky *et al.*, 1989). Supporting evidence is provided by human psychophysical studies on heat and pain sensation, using differential nerve fibre blocks (Sinclair and Hinshaw, 1950; MacKenzie *et al.*, 1975; Yarnitsky and Ochoa, 1991*a*) or using reaction times (Yarnitsky and Ochoa, 1990*a*).

Afferent channels subserved at the primary sensory neuron level by small calibre A δ

myelinated fibres may contribute to heat pain sensation. Responsiveness of A δ nociceptors stimulated by heat in animals has been clearly documented in basic studies (Georgopoulos, 1976). In rigorous studies in monkeys (Georgopoulos, 1977; Campbell and LaMotte, 1983) it was concluded that there is A δ contribution to heat pain for hairy skin, but not for glabrous skin. However, a major role for A δ nociceptors is unlikely for several reasons: (i) psychophysical studies of first and second pain produced by heat have shown that first pain, presumably mediated by A fibres, is suppressed with repeated heating (Price *et al.*, 1977); (ii) activity of C nociceptors recorded in monkeys and humans (LaMotte *et al.*, 1983; Torebjörk *et al.*, 1984; Torebjörk, 1985) best correlates with psychophysical measurements of heat pain threshold and magnitude; (iii) the heat pain threshold and the magnitude of suprathreshold heat pain are not altered significantly by the conduction block of A fibres (Torebjörk *et al.*, 1984; Yarnitsky and Ochoa, 1991*a*); (iv) at rates of temperature rise lower than 2°C per second, pain threshold is signalled by C fibre activity (Yarnitsky and Ochoa, 1990*a*). This conclusion is in keeping with the observation that heat pain evoked during quantitative sensory thermotest stimulation has a burning quality, as opposed to a sharp pricking quality. The former corresponds to excitation of C-polymodal nociceptors while the latter corresponds to excitation of A δ nociceptors in humans (Ochoa and Torebjörk, 1989).

Cold pain. Concerning the nature of the neural apparatus responsible for carrying afferent input induced by noxious low temperature ultimately evoking the sensation of cold pain, both A δ nociceptors and C-nociceptors seem to be involved, as indicated by noxious low temperature stimulus-response data gathered from recording physiologically identified single afferents in animals (Darian-Smith *et al.*, 1973; Dubner *et al.*, 1975; Georgopoulos, 1976). Comparable studies in man are remarkably uncommon (Adriaensen *et al.*, 1983). Supporting evidence for C afferent contribution to cold pain stems from human psychophysical studies during differential myelinated nerve fibre blocks (MacKenzie *et al.*, 1975; Fruhstorfer, 1976; Yarnitsky and Ochoa, 1990*b*). A few C polymodal nociceptors were reported by Torebjörk (1974) and Georgopoulos (1976) to respond to intense cooling in humans. Unreported personal observations have documented that C polymodal nociceptors, otherwise responsive to noxious mechanical and noxious heat stimuli, may or may not be responsive to noxious low temperature stimuli leading to cold pain.

The sensation of cold pain evoked by appropriately low temperature stimulation is composed of a blend of cold sensation, contributed by input along cold specific thermoreceptors, plus pain sensation contributed by nociceptors. Remarkably, upon abolition of the A δ cold specific component of 'cold pain', the magnitude of the painful component becomes disinhibited and its quality shifts to a striking burning character, in keeping with its C-nociceptor basis (Wahrén *et al.*, 1989; Yarnitsky and Ochoa, 1990*b*).

Psychophysical intensity function

The Marstock thermotest method uses subjective detection thresholds as an equivalent measure of the subjective magnitude function of somatosensory channels. The suprathreshold magnitude function is not tested by the present method, which may therefore fail to recognize instances of pure suprathreshold sensory dysfunction. A preserved detection threshold may occur in the presence of altered, exaggerated or depressed, suprathreshold magnitude estimation function (Lindblom and Ochoa, 1986).

As measured, subjective thresholds do not reflect absolute functions. They vary circumstantially depending upon a number of factors. Given the physiological dependence of most sensory submodalities upon not only *temporal* (Marks and Stevens, 1972) but also *spatial* summation, the *size* of the stimulus probe proportionally determines the quantity of afferent input, thus affecting thresholds (Lele, 1954; Kenshalo *et al.*, 1967). The rate of stimulus rise also critically influences sensory response. The faster the rate of increase in stimulus energy, the higher the frequency of firing for receptor response (Kenshalo and Duclaux, 1977; Darian-Smith *et al.*, 1979; Konietzny, 1984; Yarnitsky *et al.*, 1989, 1992). This effect, in turn, evokes a subjective response at a lowered threshold, although due to the disadvantageous operation of the reaction time artefact, the signalled threshold may become paradoxically elevated, particularly for slowly conducted afferent signals (Yarnitsky and Ochoa, 1990*a*). Methods which do not include reaction time in the measurement of threshold are not liable to this artefact. However, to a greater or lesser degree, all of these methods depart from the real measurement of absolute thresholds. Therefore, to the extent that they provide an analogue value, they are as useful as they are comprehensive and simple to apply. In this regard the Marstock method stands unrivalled.

Normal values

The normal control values presented in this work can be considered as a reference for future clinical evaluation of patients only in studies using the same method for the same sites, namely thenar and hypothenar eminences and tarsal regions. Understandably, the present values are different from those reported by Claus *et al.* (1987) for face, wrist and leg using the threshold limen method rather than individual thresholds. As mentioned above, by virtue of the spatial summation factor, the area of stimulation is a crucial determinant, particularly for the warm specific threshold. The thermode used in this study has a surface of 12.5 cm^2. This parameter is not specified by Claus *et al.* (1987). Because it affects temporal summation, rate of stimulus rise is another important factor. Our normal values were obtained with rates of approximately 2 °C/s for thermal specific sensation and 4 °C/s for thermal pain, again different from the rates used by Claus *et al.* (1987). We have observed that the relation between stimulus current and the rate of stimulus temperature change is not exactly the same for different Marstock stimulators and, therefore, the particular function must be determined for each apparatus. Baseline temperature is another important factor, as it may influence differentially the ability to discriminate a rise or fall in temperature. This effect is important even in the 'neutral zone of adapting temperature' (Darian-Smith, 1984). Given our baseline temperature of 32 °C, in comparison with that in Claus *et al.* (1987) of 35 °C, our results are biased towards a higher temperature value for cold sensation thresholds, whereas their results would favour lower values for warm sensation thresholds.

In our control population, a direct relation prevailed between age and threshold for warm specific sensation in the tarsal region, in keeping with the drop out of C unmyelinated fibres with aging (Ochoa and Mair, 1969; Jacobs and Love, 1985). This has been described by other investigations through the forced choice method (Jamal *et al.*, 1985; Mitchell and Schady, 1988; Doeland *et al.*, 1989) and is in keeping with an increase with age in the warm-cold difference limen (Fagius and Wahren, 1981). However, we did not find a significant linear relation between cold threshold and age, as described by other authors using different methods (Jamal *et al.*, 1985; Claus *et al.*, 1987).

Meaning of abnormal quantitative sensory thermotest profiles

An abnormal QST pattern usually implies the existence of a neurological disease affecting the function of somatosensory channels linked by small calibre A δ or C fibres. Thus, this method fills an information gap left unresolved by routine electrophysiological measurement of sensory nerve action potentials, which only probe large calibre myelinated fibres in peripheral nerve trunks. However, unlike sensory nerve action potentials, the QST does not localize an abnormality to the peripheral nerve fibres distal to the dorsal root ganglia. The lesion may be either in terminal nerve branches or receptors (i.e. ultradistally) at levels which escape access to sensory nerve action potential technology or in spinal roots, cord, brainstem, thalamus or cerebral hemispheres (Boivie, 1984; Boivie *et al.*, 1989; Berić, 1990).

Further, a purely psychological mechanism may decidedly account for an abnormal QST. In our patients a diagnosis of a psychogenic disorder was entertained when comprehensive neurological evaluation revealed *evidence of absence* of organic pathology that could explain the complaints of the patients plus *evidence of presence* of psychological dysfunction as their cause. Certain features of the QST profile, *per se*, suggest psychogenic origin. For example, patterns intrinsically atypical compared with either patterns commonly encountered in patients with proven organic disease or with patterns, however unusual, anticipated to be organically based through rational scientific correlation. Another feature suggesting a psychogenic basis is gross inconsistency upon retesting. A normal pattern in a normal subject or an abnormal pattern caused by an organic lesion are usually reproducible upon repetition of the test. On the other hand, when an abnormal pattern is the expression of psychogenic disorder, it is often variable and inconsistent. However, experience has proven that a bizarre pattern in an individual without evidence of organic disease and with positive evidence of psychopathology at the basis of the sensory complaints may be remarkably consistent on follow-up.

Patterns sanctioned as organic tend to be stereotyped in different individuals with similar pathophysiological states and tend to be consistent over time. They also tend to evolve into other predictable patterns as the underlying neurological disease repairs or worsens. While certain patterns convey a strong connotation of organicity, it would currently be unrealistic to qualify any pattern as absolutely organic in origin. Similarly, although in the present material there is the tendency for a correlation between psychogenicity and cold hyperalgesia, heat hyperalgesia and combined cold and heat hyperalgesia, no particular profile emerges explicitly to diagnose a psychogenic origin. As an aid, the method of Tegnér (1988), designed for tactile perception, may facilitate differentiating organic from psychogenic dysfunction through a laborious process.

Warm hypoaesthesia. Pure warm hypoaesthesia is a reassuring organically based abnormal pattern because it is common in proven organic disease and is harmonious in terms of a clinical-pathological correlation. The drop out of C unmyelinated fibres in small fibre neuropathies, of whatever cause, is expected to blunt warm sensation, while sparing thermal pains. This occurs because, as opposed to C mediated warm sensation, C mediated thermal pains have little requirement for spatial summation, i.e. the threshold function remains normal for thermal pains despite a marked depopulation of afferent fibres. Differences in the spatial summation requirement for warm sensation and for pain induced by thermal stimuli are physiologically documented (Greene and Hardy, 1958; Stevens *et al.*, 1974; Ochoa and Torebjörk, 1989; Yarnitsky and Ochoa, 1991*a*). Interestingly, for skin undergoing progressive reinnervation following severe nerve trauma, the pattern of recovery follows a reverse order, i.e. heat pain recovers before warm sensation (P. LeQuesne, personal communication, 1987), again in keeping with the lesser requirement of a dense innervation for the function of heat pain (Hardy *et al.*, 1940; Greene and Hardy, 1958; Price *et al.*, 1989).

The pattern of selective warm specific hypoaesthesia is common in aging, as found in our material and as described previously by Mitchell and Schady (1988). The progressive drop out of peripheral nerve unmyelinated fibres with aging is a well documented phenomenon (Ochoa and Mair, 1969; Jacobs and Love, 1985), although Kanda *et al.* (1991) have postulated that the changes affecting unmyelinated fibres with age occur mostly in Schwann cells.

Cold hypoaesthesia. In the context of peripheral neuropathy this pattern should correlate with selective depopulation of small calibre A δ fibres. While a few reports have been published on sensory dysfunction in individuals with selective degeneration (or agenesis?) of A δ myelinated fibres (Low *et al.*, 1978; Donaghy *et al.*, 1987), explicit descriptions of the status of warm, cold, heat pain and cold pain sensations were not detailed enough and, therefore, this clinical-pathological correlation remains to be resolved. It is unlikely that cold specific hypoaesthesia, at least in the context of peripheral nerve disease, could occur in the absence of associated cold hyperalgesia since, clinically and experimentally, a deficit of cold sensation input regularly causes cold hyperalgesia in volunteers and in patients with residual C nociceptor innervation (Wahren *et al.*, 1989; Ochoa and Yarnitsky, 1990; Yarnitsky and Ochoa, 1990*b*). If cold specific channels were selectively susceptible to system degeneration within the central nervous system (CNS), and this is unknown, isolated cold specific hypoaesthesia from CNS disease should occur.

Hypoaesthesia and hypoalgesia to thermal stimuli. Global loss for all thermal specific and thermal pain submodalities correlates with advanced damage to all fibre types in peripheral neuropathies (Hansson *et al.*, 1991). Obviously, global loss of thermal specific and thermal pain sensations is a neurological pattern not confined to peripheral nerve disease.

Heat hypoalgesia. Heat pain hypoalgesia is rarely detected in normal subjects through the present method. It should be noted, however, that this method is designed to arrest noxious heat stimuli at 50 °C, thus imposing an arbitrary ceiling which excludes normally high thresholds for heat pain. Under the same conditions, heat hypoalgesia is detected frequently in patients with warm or warm and cold hypoaesthesia. However, the fact that the anomaly is found occasionally in normal subjects tested to 50 °C prevents the determination of heat hypoalgesia in patients. Pure heat hypoalgesia is rare, even in patients, for reasons discussed above, in connection with differential spatial summation requirements for warm sensation and for heat pain.

Cold hypoalgesia. Cold pain hypoalgesia is fairly common, but not necessarily abnormal since in the population of normal individuals some do not feel cold pain as tested with transients of low temperature through the Marstock method. For this reason, an alternative potentially more useful method has been developed recently, based on measurement of latency to cold pain (D. Yarnitsky and J. L. Ochoa, unreported observations).

Thermal hyperalgesias. A major clinical yield of quantitative sensory testing is detection of cold or heat hyperalgesias, relatively common and largely neglected symptoms that reflect a challenging pathophysiological basis. We believe it fair to state that painful syndromes emanating from dysfunction of the nervous system are not completely evaluated clinically without the QST, particularly causalgiform syndromes (Lindblom and Verrillo, 1979). In addition, little sense can be made out of those syndromes, unless the QST includes the measurement of pain functions over and above measurement of cold specific and warm specific sensations. The description of two human conditions of neuropathic pain, the ABC syndrome and the CCC syndrome, characterized respectively by heat hyperalgesia and cold hyperalgesia, witnesses the crucial role of the QST in clinical routine (Ochoa, 1986; Ochoa and Yarnitsky, 1990). Further testimony includes the description of typical profiles of the QST in post-stroke chronic pain syndrome (Boivie *et al.*, 1989).

It cannot be overemphasized that fully developed heat and/or cold hyperalgesia may exist in the absence of warm or cold specific sensory deficit and in the absence of tactile deficit of any kind (Lindblom, 1985). This by itself promotes quantitative sensory testing as a more than useful test in neurological routine, provided it includes all four thermal submodalities (Asbury *et al.*, 1988). It should also be realized that this method explores the normal or abnormal physiological status of somatosensory channels rather than causal disease parameters. Therefore, it should not be expected that particular profiles of thermotest abnormality alone will provide direct clues as to the aetiology of neurological disease.

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DETERMINATION OF THE SEGMENTAL SENSORY AND MOTOR INNERVATION OF THE LUMBOSACRAL SPINAL NERVES

AN ELECTROPHYSIOLOGICAL STUDY

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SUMMARY

The knowledge of the segmental innervation of the skin and muscles of the lower limb in man is inadequate. For this reason, sensory and motor segmental innervation of the lower extremities was examined by electrophysiological methods in 27 normal subjects, one patient with possible L5 radiculopathy and one with possible lumbosacral plexus affection. Needle electrodes were placed at root levels from L3 to S2 using bony landmarks. The electrode was then placed close to the spinal nerve as indicated by a low (≤ 1 mA) threshold necessary to stimulate motor fibres. The position was controlled by X-ray in 10 subjects.

Sensory innervation was determined by recording the sensory action potential evoked by stimulating the saphenous nerve at the medial epicondyle (mainly L3 and L4) and at the medial malleolus (mainly L4 and in some L3), the medial plantar nerve at the first plantar interstice (mainly S1, some L5 and S2), the deep peroneal nerve at the first dorsal interstice (mainly L5, some S1), the sural nerve at the dorsolateral aspect of the foot (mainly S1, some L5 and S2) and at the lateral malleolus (mainly S1, some L5 and S2), and the superficial peroneal nerve at the superior extensor retinaculum (mainly L5, S1). The motor innervation was determined by stimulating the spinal nerves supramaximally and recording the evoked responses from the medial and lateral vastus (mainly L3, L4), the anterior tibial (mainly L5), the peroneus longus (L5, S1), the extensor digitorum brevis (mainly S1), the gastrocnemius (mainly S1), the abductor hallucis (mainly S2) and the biceps femoris (mainly L5, S1).

Sensory and motor conduction velocity measurements along the leg and across the lumbosacral plexus indicated that there was no difference in a disto-proximal direction, except for a 10% reduction along the most distal part of the sural nerve which, however, might be explained by utilization time. There was therefore no evidence of gradual tapering of nerve fibres in a distal direction. The proximal motor conduction velocity to the most distally placed muscle (abductor hallucis) was about 20% lower than to the proximally placed muscles (gastrocnemius and biceps femoris) suggesting a general difference in fibre calibre.

INTRODUCTION

Exact knowledge of the segmental innervation of nerves and muscles in man is important in topographical diagnosis. The current concepts of segmental innervation of the skin in man are derived mainly from the anatomo-physiological observations of Foerster (1933), the clinical observations of Head and Campbell (1900) and Keegan and Garrett (1948), and anatomical gross dissection [Bolk, 1898, 1910 (for Bolk, 1910, *see* Nieuwenhuys, 1975)]. However, the resulting outline of sensory innervation, while reasonably clear in the trunk is contradictory in the limbs. The results obtained by Foerster (1933)

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by isolating a single root, cutting several roots above and below, and determining the area of 'remaining sensibility' have shown that the total area supplied by each spinal nerve overlaps broadly with its neighbours. In contrast, Head and Campbell (1900), by evaluating the distribution of skin lesions in cases of herpes zoster involving a single nerve root, and Keegan and Garrett (1948), by analysing the area of diminished cutaneous sensitivity in cases of dorsal root compression by herniated discs, found the overlap to be scarce.

The information on the distribution of the spinal nerves to the muscles are based chiefly on clinical evidence and electrical stimulation of the roots during operations (Thage, 1965, 1974; Phillips and Park, 1991).

In the study presented in this report we have evaluated the segmental sensory and motor innervation in man from the third lumbar to the second sacral spinal nerves (L3 – S2). The sensory distribution was determined by stimulation of fibres in the sural, peroneal, medial plantar and saphenous nerves and the motor distribution by simultaneous recordings from the medial vastus, lateral vastus, anterior tibial, peroneus longus, extensor digitorum brevis, medial gastrocnemius, lateral gastrocnemius, biceps femoris and abductor hallucis. These studies provided an opportunity to study conduction in motor and sensory nerve fibres throughout the leg including the lumbosacral plexus which is usually inaccessible to detailed electrophysiological assessment.

MATERIALS AND METHODS

Subjects

The studies were performed in 27 normal subjects, 13 men and 14 women aged 20–76 yrs (average 41.6 yrs) who showed no evidence of neurological disease. In addition, two females, aged 70 yrs and 76 yrs, referred for L5 radiculopathy in one and right-sided lumbosacral plexopathy in the other, were included in the study of recording the sensory action potential at the L5–S1 spinal nerves; conduction velocities across the lumbosacral plexus were not included in the findings in this paper. The subjects lay prone. The surface temperature of the leg and the lower back was kept at 34–37°C by an infrared heat lamp controlled by a thermosensor placed on the limb. Informed consent was obtained from all subjects. No adverse effects were reported.

Position of the recording electrode at the spinal nerve controlled by X-ray (Fig. 1). The electrodes were placed close to the spinal nerves as described below. X-rays in lateral (Fig. 1) and anteroposterior views were used to ascertain the placement of the electrode with respect to the root. Comparative findings regarding segmental innervation of the skin of the lower extremity were obtained in 10 subjects in whom stimuli were applied to: (i) the saphenous nerve at the medial epicondyle; (ii) the deep branch of the peroneal nerve at the first dorsal interstice; (iii) the medial plantar nerve at the first plantar interstice; (iv) the sural nerve at the lateral malleolus; (v) the superficial branch of the peroneal nerve at the superior extensor retinaculum at the ankle. The action potentials were recorded from four different spinal levels at L3–S1 (Table 1).

In addition, the saphenous nerve was stimulated at the medial malleolus in four subjects and the sural nerve at the dorsolateral area of the foot in three subjects. The action potential was recorded at five spinal levels, L3–S2 in three of these subjects (Table 2).

Position of the recording electrode, not controlled by X-ray. In additional subjects, stimuli were applied at: (i) the saphenous nerve at the medial epicondyle and the compound sensory action potential (CSAP) was recorded at L3 and L4 (three subjects); (ii) the medial plantar nerve at the first plantar interstice with recordings at L5 and S1 (three subjects); (iii) the sural nerve at the lateral malleolus with recordings at L5 and S1 (three subjects); (iv) the sural nerve at the lateral malleolus with recordings at S1 (14 subjects); (v) the superficial branch of the peroneal nerve at the extensor retinaculum at the ankle with recordings at L5 and S1 (three subjects).

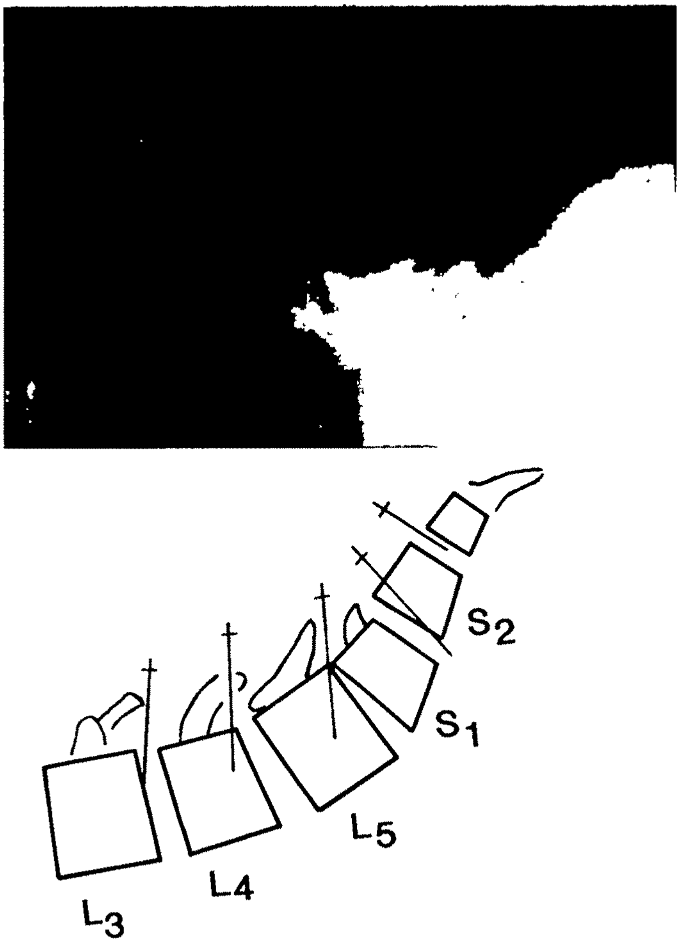

FIG. 1. *Above*: X-ray of the left lateral view to show the near nerve electrodes outside the vertebral foramen at the level of the third, fourth and fifth lumbar spinal nerves and at the level of the first and second sacral spinal nerves. *Below* diagram showing the placement of the near nerve electrodes (F.B., 25-yr-old male.)

In the 27 subjects in whom stimuli were applied at the sural nerve at the lateral malleolus, the CSAP was recorded at midcalf, popliteal fossa and gluteal crease in addition to the recording at S1. The findings in six of these subjects were included in a previous study (Horowitz and Krarup, 1992).

Placement of electrodes close to spinal nerves

The sensory response at the level of the spinal nerves and in the leg was recorded through insulated steel needles, 0.7 mm in diameter, with a 3 mm bared tip placed close to the nerve. To ensure optimal placement, the electrode was first used for stimulation and the threshold of the evoked muscle response was reduced to ≤1 mA by adjusting the position of the needle. Using this procedure the electrode is at most approximately 1 mm away from the nerve (Buchthal and Rosenfalck, 1966). The remote electrode, an insulated needle with a 5 mm bared tip, was placed subcutaneously at a transverse distance of 30–40 mm. To reduce the impedance of the electrodes they were current treated in saline at 90°C before use (Buchthal and Rosenfalck, 1966).

TABLE 1. SEGMENTAL SENSORY REPRESENTATION IN TEN SUBJECTS

	Recording sites of spinal nerve action potentials			
Site of stimulation	*L3*	*L4*	*L5*	*S1*
Medial epicondyle[1]	10	10	2	0
First dorsal interstice[2]	0	0	10	4
First plantar interstice[3]	0	0	8	10
Lateral malleolus[4]	0	0	3	10
Retinaculum superior[5]	0	1	10	10

Stimulation of: [1]the saphenous nerve at the medial epicondyle; [2] the deep peroneal nerve at the first dorsal interstice; [3]the medial plantar nerve at the first plantar interstice; [4]the sural nerve at the lateral malleolus; [5]the superficial peroneal nerve at the superior extensor retinaculum at the ankle. The evoked sensory action potentials were recorded at the L3–S1 spinal nerves.

The spinous process of the L4 vertebra at level with the highest points of the iliac crests was used for gross orientation to insert a needle-electrode close to the spinal nerve. The CSAP from the L3 spinal nerve was recorded through an electrode inserted 3–4 cm lateral to the L4 spine with the needle passing above the L4 transverse process (Fig. 1). To record from the L4 and L5 spinal nerves, the electrodes were inserted about 3 cm and 5 cm below the L4 spinal process, respectively, and 3–4 cm lateral to a line connecting the spinous processes. The electrode used to record from the S1 spinal nerve was inserted through the skin slightly medial and caudal to that used for L5, directed caudally, and pushed through into the first sacral foramen. To record from the S2 spinal nerve the electrode was inserted 3–4 cm below the position of the L5 spinal nerve and 1.5–2 cm lateral to the midline. The depth of insertions from the skin was 70–90 mm for L3–S1 spinal nerves and approximately 40 mm for S2 spinal nerve.

In addition to recording the CSAP at the spinal nerves, the sural CSAP from the sural nerve at the lateral malleolus was recorded at the midcalf, popliteal fossa and the gluteal crease.

Evaluation of the segmental sensory innervation

Sites of stimulation. The sural nerve at the lateral malleolus, the peroneal nerve at the superior extensor retinaculum, and the saphenous nerve at medial epicondyle were stimulated through an insulated steel needle electrode 0.7 mm in diameter with a 3 mm bared tip placed close to the nerve. The anode, with a 5 mm bared tip, was inserted subcutaneously at a longitudinal or transverse distance of 2–3 cm. The deep branch of the peroneal nerve at the first dorsal interstice, the medial plantar nerve at the first plantar interstice, the saphenous nerve at the medial malleolus and the sural nerve at the dorsolateral area of the foot were stimulated through a bipolar surface electrode with a distance of 2.5 cm between the proximal cathode and the anode.

The stimulus was a rectangular pulse, 0.2 ms in duration, from a constant current stimulator given at a rate of 1–3/s. The sensory threshold for the electrical stimulus was determined and a painless stimulus intensity was usually set 2.5 times above this level.

Recording of the CSAP. The CSAP was amplified (DANTEC 15C02, 200–2000 Hz or 4000 Hz, 3 dB down), averaging (64–1000 responses, sampling rate 40 μs), and recorded on an ink-jet writer (Siemens Mingograf) via a digital memory store (event or transient recorder) (Dahl and Buchthal, 1978). The maximum sensory conduction velocity was determined from the latency to the first reproducible positive peak of the CSAP. The reproducibility was ascertained by doubling the number of responses (Fig. 2). The amplitude was measured peak-to-peak. The most important error in the interpretation of the segmental representation is conduction in volume to adjacent spinal nerves of potentials from the nerve(s) which receives most or all sensory fibres. The response was considered volume conducted if the potential was of low amplitude (≤ 0.2 μV) and the negative phase had a slow rise time. In cases where the response was thought to be volume conducted from spinal nerves at a distance from the recording electrode, its amplitude was less than 10% of the maximal response.

TABLE 2 SEGMENTAL SENSORY REPRESENTATION AND AMPLITUDE OF SPINAL SENSORY POTENTIALS IN ALL SUBJECTS

	Recording sites of spinal nerve action potentials				
Site of stimulation	*L3*	*L4*	*L5*	*S1*	*S2*
Medial epicondyle[1]					
Number of subjects	13/13	13/13	2/10	0/10	0/3
mean amplitude	0.6	0.8	1.5	—	—
range	0.2−1.3	0.2−2.8	0.6−2.4		
Proximal medial malleolus					
Number of subjects	3/4	4/4	1/4	0/4	0/3
mean amplitude	0.6	0.4	0.3	—	—
range	0.2−0.8	0.3−0.8	—	—	—
First dorsal interstice[3]					
Number of subjects	0/10	0/10	10/10	4/10	0/3
mean amplitude	—	—	0.4	0.8	—
range	—	—	0.3−0.6	0.5−0.9	—
First plantar interstice[4]					
Number of subjects	0/10	0/10	10/13	13/13	2/3
mean amplitude	—	—	0.5	0.7	0.8
range	—	—	0.3−0.7	0.2−2.4	0.5−1.2
Dorsolateral foot[5]					
Number of subjects	0/3	0/3	2/3	3/3	2/3
mean amplitude	—	—	0.7	0.4	0.6
range	—	—	0.3−1.2	0.2−0.5	0.5−0.8
Lateral malleolus[6]					
Number of subjects	0/10	0/10	7/13	27/27	2/3
mean amplitude	—	—	0.8	1.2	1.2
range	—	—	0.2−1.9	0.2−3.2	0.8−1.5
Retinaculum superior[7]					
Number of subjects	0/10	1/10	13/13	13/13	0/3
mean amplitude	—	0.6	0.7	0.5	—
range	—	—	0.2−2.4	0.2−1.2	—

Stimulation of: [1]the saphenous nerve at the medial epicondyle; [2]the saphenous nerve at the medial malleolus; [3]the deep peroneal nerve at the first dorsal interstice; [4]the medial plantar nerve at the first plantar interstice, [5]the sural nerve at the lateral edge of the foot; [6]the sural nerve at the lateral malleolus; [7]the superficial peroneal nerve at the superior extensor retinaculum at the ankle. The evoked sensory action potentials were recorded at the L3−S1 spinal nerves. The number of subjects indicates the number with a CSAP at the spinal nerve compared with the total number tested. The mean amplitude (μV) was calculated from subjects with a response

Evaluation of the segmental motor innervation

Sites of stimulation and recording of the evoked motor response. Supramaximal stimuli were delivered via the same needle electrodes used for recording the CSAP. The L3−L5 spinal nerves were stimulated in 10 subjects, the S1 in 11 subjects and the S2 in three subjects. In order to calculate conduction velocities, stimulation was also performed at popliteal fossa and at gluteal crease. Simultaneous recordings were obtained from the medial vastus, lateral vastus, anterior tibial, peroneus longus, extensor digitorum brevis, medial gastrocnemius, lateral gastrocnemius, biceps femoris and abductor hallucis muscles

Recording of the compound motor action potentials (CMAP). Motor action potentials were recorded via surface electrodes placed over the end plate zone in a belly-tendon montage, amplified (DANTEC 15C01, 20 Hz−10 kHz, 3 dB down), and recorded via a 14-channel event recorder on an ink-jet writer

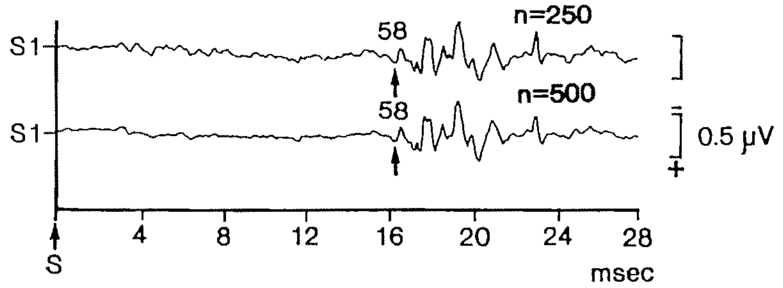

FIG. 2. Orthodromic compound sensory action potentials (CSAP) recorded from S1 spinal nerve evoked by stimulation of the superficial peroneal nerve at the superior extensor retinaculum. n = number of stimuli. To distinguish the initial components, the responses to 250 and 500 stimuli were averaged S denotes the onset of the stimulus. The latency was measured to the arrow and the conduction velocity in metres per second is indicated above the traces. (F B., 25-yr-old male.)

(Dahl and Buchthal, 1978). The motor latency to the initial negative deflection from the baseline of the CMAP and the amplitude of the negative phase were measured. Maximal responses with a negative onset and amplitude greater than 0.3 mV were considered to indicate that the CMAP originated from the muscle over which the electrode was placed rather than from nearby muscles innervated by the spinal nerve being stimulated. In the remaining 19 subjects motor responses were recorded through concentric needle electrodes. Since the amplitudes and latencies of CMAPs between different muscles and different subjects cannot be directly compared with results obtained by surface electrodes, the results of recordings with concentric needles have not been used to ascertain the relative contribution of different spinal nerves. However, the maximal conduction velocities between stimulation sites across the lumbosacral plexus and along the thigh were calculated using both surface and concentric electrodes.

Conduction distance

Distances were determined from the site of stimulation to the recording electrode using a tape measure along the leg and a caliper from the gluteal crease to the spinal nerve. The electrodes close to the S1 and S2 spinal nerves were placed at an angle with respect to the surface. The distance from perpendicular was estimated from the X-rays and ranged from 8 mm to 38 mm (average 30 mm). The distance to these spinal nerves was therefore corrected by subtracting 30 mm from the surface measurement values.

RESULTS

Segmental sensory innervation

Stimuli to the saphenous nerve at the medial epicondyle (Tables 1, 2, Fig. 3) evoked a response at L3 and L4 in all 13 subjects. In 20%, a response was present in addition at the level of L5. Recordings at the levels of S1 and S2 showed no responses.

Stimuli to the saphenous nerve at medial malleolus (Table 2) evoked a response in all four subjects at the level of L4, in 75% at the level of L3, and in 25% at L5. Only one of the two subjects with a response at L5 evoked at the medial epicondyle was studied from the medial malleolus. Recordings at the level of S1 and S2 showed no responses.

Stimuli to the deep branch of the peroneal nerve at first dorsal interstice (Tables 1, 2, Fig. 4) evoked a response in all 10 subjects at the level of L5 and from 40% at S1. Recordings at the levels of L3, L4 and S2 showed no responses.

Stimuli to the medial plantar nerve at first plantar interstice (Tables 1, 2, Fig. 4) evoked a response in all 13 subjects at the level of S1, in 77% at the level of L5 and in 67%

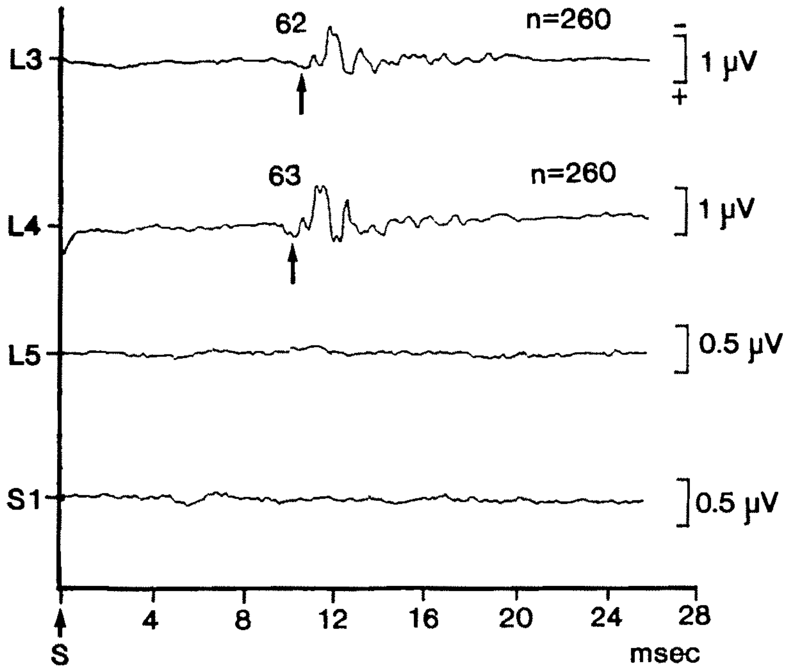

FIG. 3. Orthodromic CSAPs at the level of the third and fourth lumbar spinal nerves evoked by stimulation of the sapheneous nerve at medial epicondyle The spinal nerve potentials had about the same amplitude at L3 and L4 and could not be distinguished at L5 and S1. n = number of stimuli. S denotes the onset of the stimulus. The latency was measured to the arrow and the conduction velocities in metres per second are indicated above the traces (K.S., 27-yr-old male.)

at the level of S2. Recordings at the levels of L3 and L4 spinal nerves showed no responses.

Stimuli to the sural nerve at the dorsolateral area of the foot (Table 2) evoked a response in all three subjects at the level of S1 and in 67% at the level of L5 and S2. In no subject was there a response at the level of L3 and L4 spinal nerves.

Stimuli to the sural nerve at lateral malleolus (Tables 1, 2, Fig. 5) evoked a response in all 27 subjects at the level of S1, in 54% at the level of L5 and in 67% at the level of S2. Recordings at the levels of L3 and L4 showed no responses.

Stimuli to the superficial peroneal nerve at the superior extensor retinaculum (Tables 1, 2, Fig. 6) evoked a response in all 13 subjects at the level of L5 and S1. Additionally, in 10% a response was present at the level of L4. Recordings at the levels of L3 and S2 showed no responses.

Conduction properties of CSAP

The amplitude of the CSAP recorded at the spinal nerves ranged from 0.2 μV to 3.2 μV (Table 2), and was dispersed in shape. There was no relationship between the average amplitude and the distance to the site of stimulation (Fig. 7A), though the potential appeared less dispersed at proximal (Fig. 3) than at distal stimulation (Fig. 5). The latency of the response increased linearly with conduction distance (Fig. 7B).

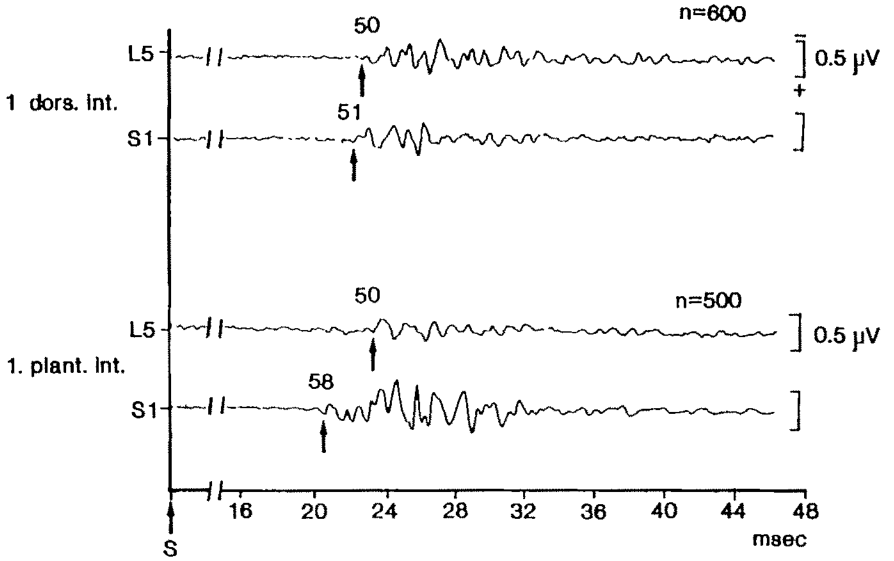

FIG 4. Orthodromic CSAPs recorded at the level of the fifth lumbar and first sacral spinal nerves evoked by stimulation to first dorsal interstice (upper two traces) and to first plantar interstice (lower two traces). The CSAPs recorded at L5 and S1 and evoked by stimuli to first dorsal interstice had about the same amplitude. Stimulation of the first plantar interstice evoked responses at both spinal nerves but the amplitude was highest at S1. n = number of stimuli. S denotes the onset of the stimulus. The latency was measured to the arrow and the conduction velocities are indicated above the traces in metres per second. (F.B., 25-yr-old male.)

Stimulating the sural nerve at the malleolus lateralis, the CSAP was recorded at the midcalf, popliteal fossa, the gluteal crease and the spinal nerves (Fig. 5). The average amplitude of the response decreased sharply at short distances and then levelled off as a power function of the conduction distance; the latency increased linearly with the conduction distance (Fig. 8). The slope of the regression line corresponded to a constant conduction velocity of 61.4 m/s. However, when the conduction velocities along different segments of the nerve were compared, the conduction velocity along the most distal segment from ankle to midcalf (52.9 ± 0.7 m/s) was about 10% lower (Fig. 9) than along more proximal segments ($P = 0.004$, ANOVA). No statistical difference in conduction velocity was found between the segments midcalf to popliteal fossa (58.6 ± 1 m/s), popliteal fossa to gluteal crease (59.5 ± 1.3 m/s) and gluteal crease to S1 (57.3 ± 1.8 m/s).

Segmental motor innervation

The results of simultaneous recordings with surface electrodes from lower limb muscles during electrical stimulation of L3, L4, L5 and S1 spinal nerves (Fig. 10) have been compiled in Table 3. Additionally, the S2 spinal nerve was stimulated in three subjects.

Stimulation at L3 and L4 evoked a CMAP in the medial vastus muscle (2.4–11 mV and 1.5–15 mV, respectively) and the lateral vastus muscle (1.6–10 mV and 1.4–15 mV, respectively) of all 10 subjects. In the medial vastus the response was larger at stimulation of L3 in three and at L4 in two subjects. In the lateral vastus the

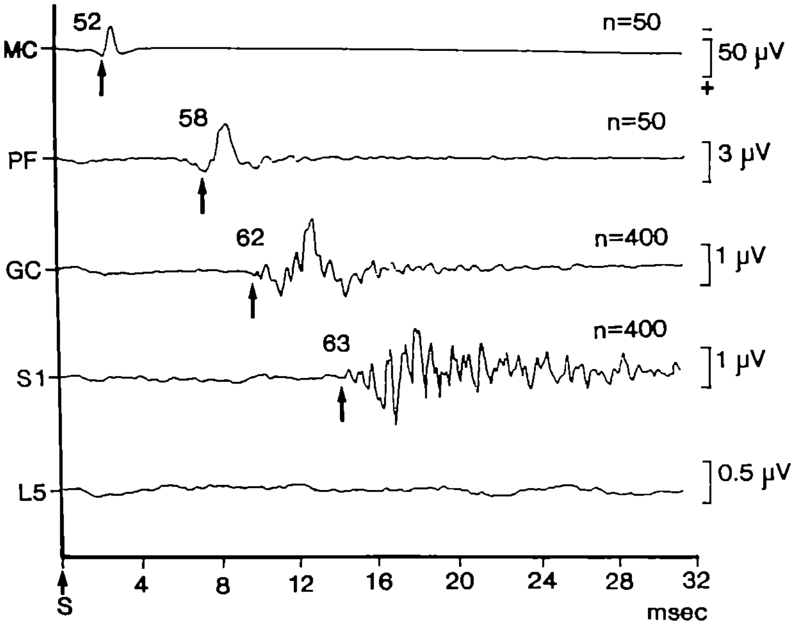

FIG. 5. Orthodromic CSAPs recorded at midcalf (MC), popliteal fossa (PF), gluteal crease (GC) and at the level of the first sacral spinal nerve evoked by stimulation of the sural nerve at malleolus lateralis. n = number of stimuli S denotes the onset of the stimulus The latency was measured to the arrow and the conduction velocities in metres per second are indicated above the traces. (B.I., 48-yr-old female.)

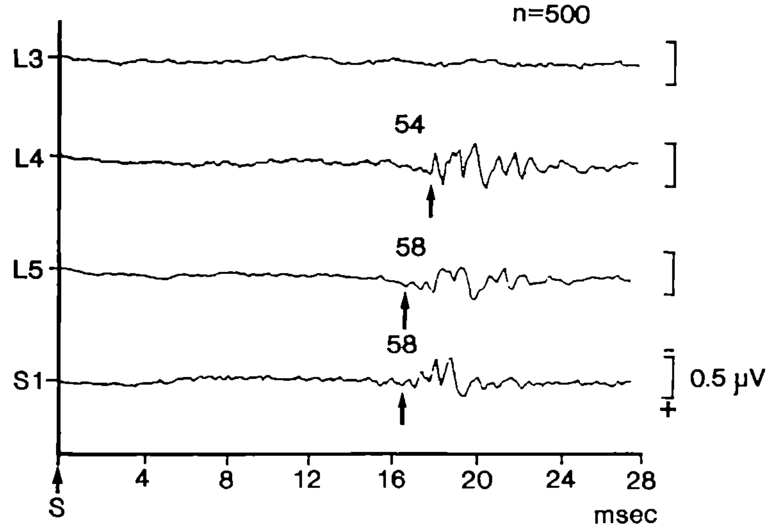

FIG. 6. Orthodromic CSAPs at the level of the fourth and fifth lumbar spinal nerves and first sacral spinal nerve evoked by stimuli to superior extensor retinaculum. Spinal nerve potentials had about equal amplitude at L4, L5 and S1. No response could be detected at L3. n = number of stimuli S denotes the onset of the stimulus The latency was measured to the arrow and the conduction velocities in metres per second are indicated above the traces. (B.J., 23-yr-old female.)

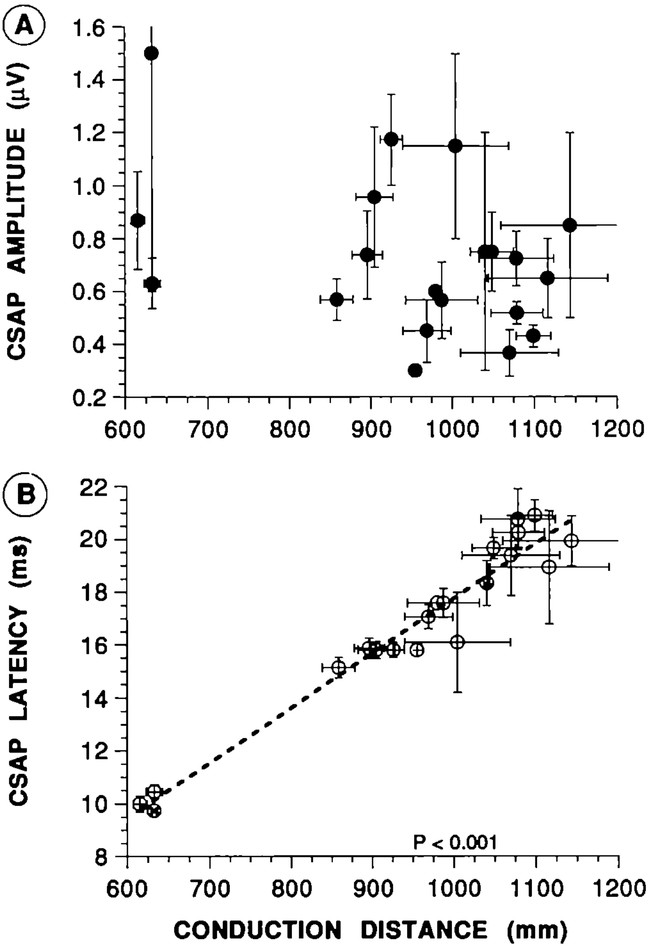

FIG. 7. Mean amplitude (A) and latency (B) of the orthodromic CSAPs evoked at distal sites (the sural nerve at lateral malleolus and dorsum pedis, the peroneal nerve at the superior extensor retinaculum and the first dorsal interstice, the saphenous nerve at medial epicondyle and the medial malleolus, and the medial plantar nerve at the first plantar interstice). The error bars denote the SEM. The regression curve in B was calculated using the least square method ($r = 0.9730$, $P < 0.001$).

response was larger at stimulation of L4 in two subjects and at stimulation of L3 in one subject. In two subjects stimulation at L5 evoked a CMAP in medial vastus (0.9 mV and 15 mV) and the lateral vastus (1 mV and 15 mV). Stimulation of S1 and S2 did not evoke a response in the medial vastus or lateral vastus of any subject.

Stimulation at L4 evoked a CMAP (0.5–2.1 mV) in the anterior tibial muscle in seven and at L5 (0.5–5.5 mV) in nine subjects. In three of the six subjects with responses from both roots, stimulation of L5 evoked a larger response than stimulation of L4. In one subject the muscle was monosegmentally innervated from L4 and in two from L5. A contribution from S1 occurred in two subjects (0.8 mV and 2.5 mV), in one together with L5 and in one with L4 and L5. Stimulation of L3 and S2 did not evoke a response in the anterior tibial of any subject.

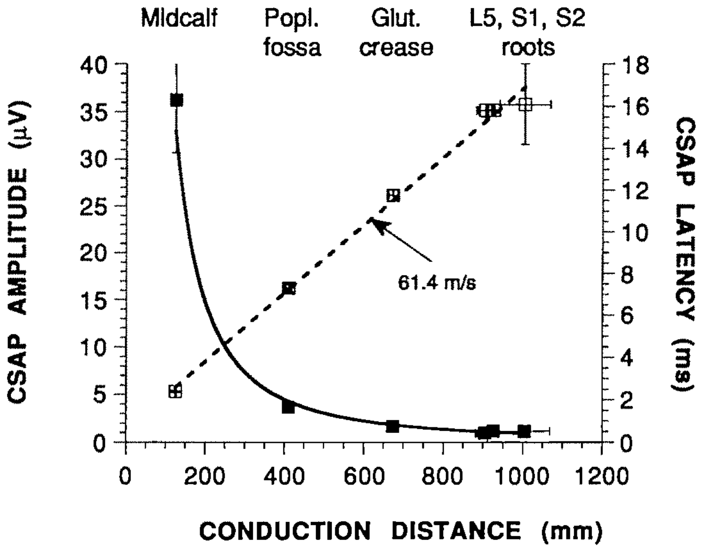

FIG. 8. Mean amplitude (closed squares) and latency (open squares) of the sural nerve orthodromic CSAPs evoked by stimulation at the lateral malleolus. Recordings were carried out at midcalf, popliteal fossa, gluteal crease and the L5, S1 and S2 spinal nerves. The regression curves were calculated using the least squares method. The amplitude was described by a power function (Amplitude $= 1.35 \times 10^5 \times \text{Distance}^{-1.72}$, $r = -0.9995$, $P < 0.001$) and the latency by a linear function ($r = 0.9966$, $P < 0.001$) with a slope corresponding to a conduction velocity of 61.4 m/s. The error bars denote the SEM.

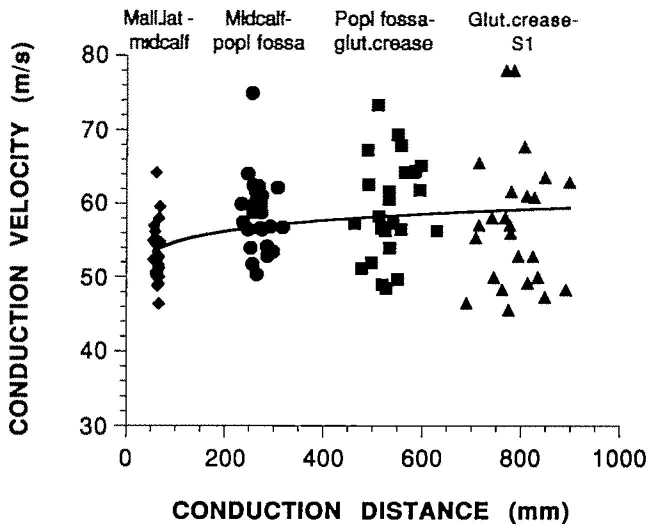

FIG. 9 Conduction velocities of the orthodromic CSAPs along the sural nerve as a function of the distance in a proximal direction The nerve was stimulated at the lateral malleolus and the responses recorded at the midcalf, popliteal fossa, gluteal crease and the S1 spinal nerve. The conduction velocities were calculated between the stimulus and recording site for the most distal segment (closed diamonds) and from the differences in conduction time at the other recording sites. The distances are indicated to the midpoint between the stimulus-recording sites or two subsequent recording sites. The power function was calculated using the least-squares method ($r = 0.3151$, $P < 0.01$)

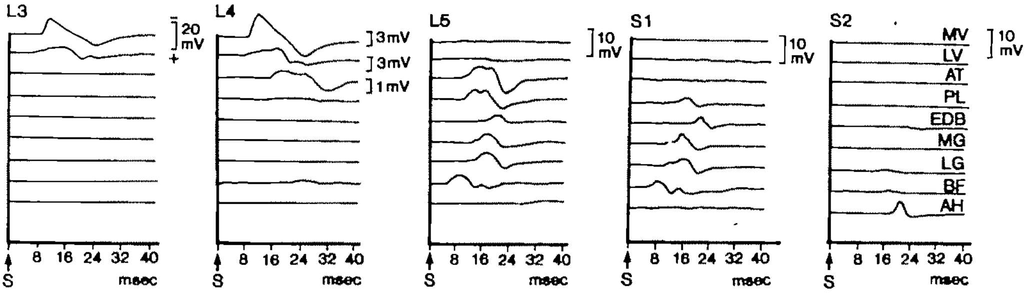

FIG. 10. Compound muscle action potentials recorded from the MV, medial vastus; LV, lateral vastus; AT, anterior tibial, PL, peroneus longus; EDB, extensor digitorum brevis; MG, medial gastrocnemius; LG, lateral gastrocnemius, BF, biceps femoris; AH, abductor hallucis muscles evoked by stimulation at L3, L4, L5, S1 and S2 in a normal subject. (H.B., 31-yr-old male.)

TABLE 3 SEGMENTAL MOTOR REPRESENTATION IN 10 SUBJECTS

	Stimulation sites of spinal nerves			
Site of recording	*L3*	*L4*	*L5*	*S1*
MV	10	10	2	0
LV	10	10	2	0
AT	0	7	9	2
PL	0	0	9	10
EDB	0	0	8	10
MG	0	0	8	10
LG	0	0	8	10
BF	0	3	10	10
AH	0	0	2	7

MV = medial vastus; LV = lateral vastus, AT = anterior tibial; PL = peroneus longus; EDB = extensor digitorum brevis, MG = medial gastrocnemius; LG = lateral gastrocnemius; BF = biceps femoris; AH = abductor hallucis

Stimulation at L5 evoked a CMAP (0.8–7.5 mV) in the peroneus longus muscle in nine and at S1 (1–7 mV) in all 10 subjects. In three subjects the amplitude of the CMAP was greatest at stimulation of L5 and in two subjects at stimulation of S1. Stimulation of L3, L4 and S2 did not evoke a response in any subject.

Stimulation at L5 evoked a CMAP (0.8–4.2 mV) in the extensor digitorum brevis muscle in eight and S1 (0.5–4 mV) in all 10 subjects. In two of three subjects, stimulation at S2 evoked a response (3.6 mV and 4 mV). The largest CMAP amplitude was obtained during stimulation of L5 in three subjects, S1 in one subject and S2 in one subject. Stimulation of L3 and L4 did not evoke a response in any subject.

Stimulation at L5 evoked a CMAP in the medial gastrocnemius muscle (1.5–10 mV) and the lateral gastrocnemius muscle (2–14 mV) in the same eight subjects. Stimulation at S1 evoked a CMAP in all 10 subjects in both the medial gastrocnemius (2.8–14 mV) and the lateral gastrocnemius (4–17 mV). In two of three subjects, stimulation at S2 evoked a response in the medial gastrocnemius (3.3 mV and 9 mV) and the lateral gastrocnemius (2.5 mV and 2.7 mV). In eight subjects the CMAP amplitude in both the medial gastrocnemius and the lateral gastrocnemius evoked by stimulation of S1 was larger than that evoked by stimulation of L5. Stimulation of L3 and L4 did not evoke a response in any subject.

Stimulation at L5 and S1 evoked a CMAP (1.8–8.5 mV and 1–5.7 mV, respectively) in the biceps femoris muscle of all 10 subjects. Responses were also obtained at stimulation of L4 (2.2–4 mV) in three subjects and at stimulation of S2 (0.8 mV and 0.9 mV) in two subjects. The largest amplitude was obtained in four subjects by stimulation at L5 and in two subjects at S1. Stimulation of L3 did not evoke a response in any subject.

Stimulation at S1 evoked a CMAP (0.3–3.5 mV) in the abductor hallucis muscle in seven subjects. In two of these stimulation of L5 evoked a response (0.5 mV and 0.8 mV), and at stimulation of S2 in another of these seven subjects a response was present (6.3 mV). In three subjects there was no response either from L5 or from S1. The S2 root was stimulated in two of these three subjects and the response (3.6 mV and 5.5 mV) indicated that the muscle was monosegmentally innervated. Stimulation of L3 and L4 did not evoke a response in any subject.

Conduction properties of the CMAP

The amplitude of the negative phase of the CMAP evoked at different roots varied widely but had no relationship with the conduction distance (Fig. 11A). In contrast, the CMAP recorded from the medial and lateral gastrocnemius muscle decreased more than 50% when the distance was increased by stimulating the nerve at the popliteal fossa, gluteal crease and the L5, S1 and S2 roots (Fig. 11B). Summing the amplitudes of the CMAPs evoked at the different spinal levels (Fig. 11B) indicated that the lower amplitude at stimulation at the spinal nerves was in part due to temporal dispersion and in part to the multilevel innervation of the muscle. The sum of the amplitudes was similar to the response evoked at the popliteal fossa. The slope of the linear relationship of the latency versus distance corresponded to a conduction velocity of 58.7 m/s. When the two segments from the S1 spinal nerve to the gluteal crease (56.6 ± 1.7 m/s) and from the gluteal crease to the popliteal fossa (61 ± 2.1 m/s) were compared there was no statistical difference ($P = 0.2$, paired t test). The motor conduction velocity from S1 to the gluteal crease along fibres to the biceps femoris was 59.5 ± 3.3 m/s. In an ANOVA test of these conduction velocities across the plexus and along the thigh no statistical difference was found ($P = 0.2$). In contrast, the conduction velocity across the plexus along fibres to the abductor hallucis, 45 ± 4.3 m/s ($n = 6$) was significantly lower ($P = 0.02$, ANOVA, repeated measures) than to the more proximal muscles.

DISCUSSION

Segmental innervation of the lower limb

In this study the sensory and motor segmental innervation of the lower extremities has been delineated using electrodes placed close to the spinal nerves just outside the intervertebral foramina. Inouye and Buchthal (1977) used a similar method to examine the segmental sensory innervation in the upper extremities; however, they did not describe the motor innervation from the cervical spinal cord. The near-nerve electrodes have the advantage that small sensory potentials of less than 0.1 μV may be recorded when electronically averaged (Behse and Buchthal, 1978; Buchthal *et al.*, 1984), thus allowing the dispersed responses evoked by stimulation even at the big toe to be distinguished

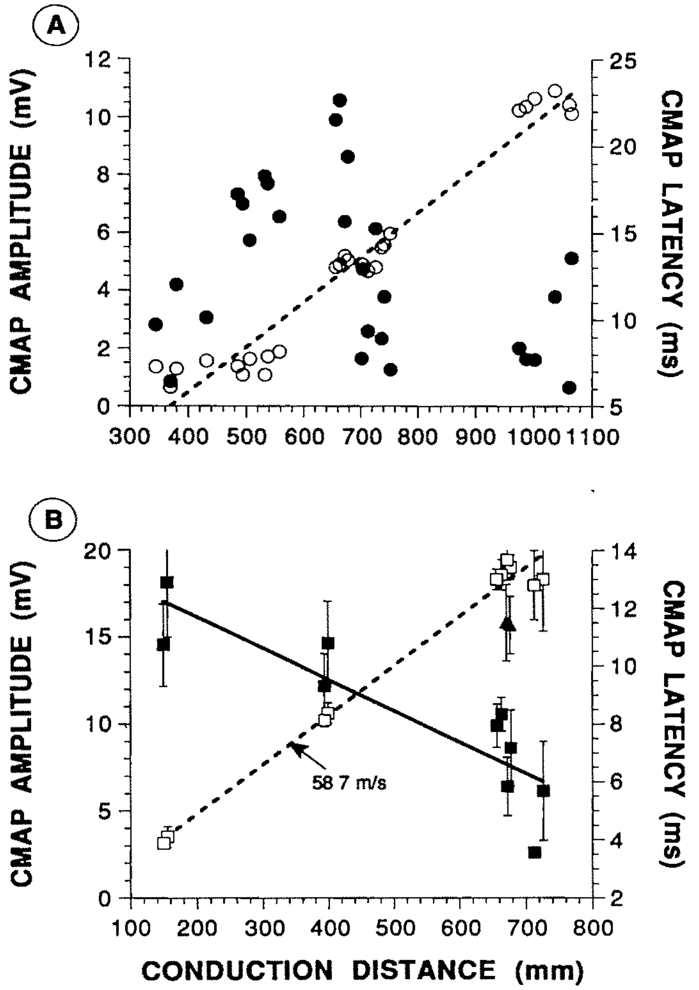

FIG. 11. A mean amplitude (closed circles) and latency (open circles) of the CMAPs evoked by stimulation at the L3, L4, L5, S1 and S2 spinal nerves and recorded from the medial vastus, lateral vastus, anterior tibial, peroneus longus, extensor digitorum brevis, medial gastrocnemius, lateral gastrocnemius, biceps femoris and abductor hallucis muscles. The linear regression curve for the latencies was calculated using the least squares method ($r = 0.9761$, $P < 0.01$). Error bars have been excluded for clarity B, mean amplitude (closed squares) and latency (open squares) of the CMAPs, evoked by stimulation at the popliteal fossa, the gluteal crease and the L5, S1 and S2 spinal nerves and recorded from the lateral and medial gastrocnemius muscles. The closed triangles indicate the sum of the CMAPs in the two muscles evoked by stimulation at the three roots. The linear regression curves were calculated by the least squares method (amplitude $r = -0.8770$, $P < 0.001$; latency $r = 0.9912$, $P < 0.001$, slope corresponding to a conduction velocity of 58.7 m/s). The error bars denote the SEM.

from noise. The disadvantage of the technique is the possibility of recording sensory action potentials at a given site which in fact originate from neighbouring spinal nerves, inside or outside the vertebral canal. However, responses recorded over a distance of 1 cm or more have slow rise times in addition to a marked attenuation of amplitude (Inouye and Buchthal, 1977). Considering an attenuation of 70–80% per centimetre distance from the generator source (Buchthal and Rosenfalck, 1966), the amplitude of the potential approximately 3 cm from the spinal nerve would be at most 0.1 μV. In this study we have limited the accepted amplitude of CSAPs originating from the spinal nerve closest to the recording electrode to 0.2 μV.

By placing the stimulating electrode close to the spinal nerve as indicated by a threshold of the evoked CMAP of <1 mA, maximal responses can be elicited by current pulses of relatively low amplitude not expected to elicit activity in neighbouring nerves. This advantage allows more precise determination of segmental motor innervation than the method of high current stimulation through a monopolar needle placed at a distance from the spinal nerves at the cervical or lumbosacral spine (MacLean, 1980). In our study we have used surface electrodes with a large recording area to delineate the muscles activated from a given root. Such electrodes have the advantage that the amplitude of the CMAP from large muscles, for example the medial and lateral vastus, give a better relative measure of the proportion of motor units activated than a concentric needle, due to the dependence of the spike amplitude on the position of the electrode. The disadvantage of the surface electrode is related to the possibility of picking up from nearby muscles. Recording from other muscles is avoided using a concentric needle but a small contribution from motor units at some distance from the electrode may be missed. In this study we considered the lower limit of 0.3 mV to be a criterion that the response was derived from the muscle over which the electrode was placed.

Different methods have, in the past, been used to examine the segmental sensory innervation of the skin of the lower extremities in man:

Anatomical dissection. Bolk (1898) dissected the body of a 3-yr-old boy and followed the nerves from the vertebral foramina distally through the lumbosacral plexus to determine the course of individual segmental distributions [*cf* Nieuwenhuys 1975 reprint of Bolk's (1910) figures].

Distribution of herpes zoster lesions. It has long been recognized (*cf* Hansen and Schliack, 1962, p. 31) that the distribution of the herpes zoster eruption follows the sensory innervation of the skin in peripheral nerve and has been used to trace the innervation areas of particular peripheral nerves (Perroud, 1876–1877). Head and Campbell (1990) examined the spinal segmental distribution of 394 cases of herpes zoster eruptions and mapped the segments on the surface of the body. Of these, nine cases were localized to L3, L4, L5 and S2, whereas there were none to S1. They write, '. . . to each segment was given a hypothetical number which was supposed to represent its numerical localisation in the central nervous system. This numerical localisation met with universal disbelief, alike from anatomists and clinicians, and it was therefore felt that if a post-mortem examination could be obtained on a case of herpes zoster in which the distribution of the eruption had been carefully drawn or photographed, the question might be settled one way or the other' (pp. 395–396). For example, Brissaud (1896*a*,*b*) found that the zoster eruption, 'zona', on occasion did not follow the sensory radicular distribution and suggested a 'segmental' central nervous system in addition to a radicular segmental innervation. These differences were thought to be associated with the relative ascent of the spinal cord during foetal development and postnatal growth. Head and Campbell (1900) carried out post-mortem examinations in 21 cases and found that the skin lesion closely corresponded to the affected dorsal root ganglion. However, only one case was localized to L1 and none were below this level. Hansen and Schliack (1962) also examined herpetic eruptions from L1 to S1 but had no case from L5 and did not confirm the postulated level by post-mortem in any of their cases. A degree of uncertainty regarding the segmental innervation of the lower extremities is inherent in these studies since the eruption on the skin was not localized by anatomical methods at the spinal level below L1.

Remaining sensibility. Foerster (1933) examined the sensibility which remained '. . . after contiguous roots had been divided, and a single root in the middle of them had been left intact'. He described the segmental innervation of the whole lower extremity from L1 to S2 and for several segments confirmed the anatomical distribution found by Head and Campbell (1900).

Hypalgesia after individual root lesions. Foerster (1933) in single root lesions did not find sensory loss except when using detailed quantitative sensory examination. By contrast, Keegan and Garrett (1948) found lower extremity L3–S2 dermatome hypalgesia in 1264 cases (707 verified by surgery) of 1342 single root lesions helpful in the delineation of segmental innervation.

Considering the different approaches and the studies of patients with different lesions of the peripheral and central nervous system, it is perhaps not surprising that there is considerable disagreement in the literature regarding the extent and distribution of individual dermatomes (*cf* Keegan and Garrett, 1948). The segmental distribution derived from spinal nerve sensory potentials recorded in a limited number of subjects in our study indicates a considerable degree of overlap between neighbouring dermatomes. In other studies, the degree of overlap between different dermatomes varies considerably. Although Foerster (1933) found a variable degree of overlap, the clinical studies of Head and Campbell (1900) and Keegan and Garrett (1948) found the overlap to be less conspicuous. Foerster (1933) also described individual variations, for example that the third lumbar spinal nerve may supply either the proximal inner side of the leg or may extend below as far as the medial malleolus. However, information concerning the number of patients in whom each dermatome was localized or how often the variation occurred was not given, and the method of 'remaining sensibility' gives no information as to whether a given sensory area connects to more than one root.

We found a substantial individual variation when stimulating cutaneous areas (Table 4). Recording of the CSAP at multiple spinal nerves moreover indicates that more than

TABLE 4 SEGMENTAL SENSORY AND MOTOR INNERVATION OF THE LOWER EXTREMITY

Skin area sensory innervation	*Spinal segment*	*Muscle motor innervation*	*Spinal segment*
Medial area of knee	**L3**, **L4**, (L5)	Quadriceps	**L3**, **L4**, (L5)
Anteromedial area of ankle	L3, **L4**, (L5)	Anterior tibial	L4, **L5**, (S1)
First dorsal interstice	**L5**, S1	Peroneus longus	**L5**, **S1**
First-plantar interstice	L5, **S1**, S2	Extensor digitorum brevis	L5, **S1**, S2
Dorsolateral area of the foot	L5, **S1**, S2	Gastrocnemius	L5, **S1**, S2
Posterolateral area of ankle	L5, **S1**, S2	Abductor hallucis	(L5), S1, **S2**
Anterolateral area of ankle	(L4), **L5**, **S1**	Biceps femoris	L4, **L5**, **S1**, S2

When the number of subjects was ≥90% at a given area or muscle, the segment is printed in **bold**; when the number was ≥33% and <90%, the segment is printed in ordinary print, and when the number was <33%, the segment is shown in parentheses.

one spinal nerve often connects to a given cutaneous area. For example, the medial area of the knee was innervated by L3 and L4 in all subjects and in some additionally by L5. In other studies opinions differ with respect to the cutaneous areas supplied by L4: Foerster (1933) and Keegan and Garrett (1948) thought that connections extended along the inner side of the leg and foot including the first dorsal and first plantar interstices, whereas according to Head and Campbell (1900) and Bolk (1910, *cf* Nieuwenhuys, 1975), the big toe is not innervated by L4. We found the medial area of the ankle to be innervated mainly by the L4 root (Table 4) but that L4 never extended to the dorsum of the big toe which was innervated mainly by L5 or by L5 and S1. The plantar side of the big toe was innervated by S1 in all subjects and additionally by L5 or S2 in some subjects.

Disagreement is present in assigning the territory of the second sacral dermatome as well. Foerster (1933) thought that the S2 supplied the sole of the foot and the plantar and dorsal aspects of the toes in addition to other cutaneous areas. In the subjects investigated by Head and Campbell (1900), Foerster (1933) and Keegan and Garrett (1948) the distribution of S2 dermatome never extended to the dorsolateral side of the foot. In contrast, Bolk (*cf* Nieuwenhuys, 1975) assigned the distribution of S2 dermatome of the foot to the lateral side of the foot and small toe only. We recorded CSAPs from the S2 spinal nerve in only three subjects and found that the distribution of S2 dermatome may comprise a wide cutaneous area from the first plantar interstice across the plantar aspect to the dorsolateral side of the foot to the posterolateral aspect of the ankle. The anterolateral aspect of the ankle was innervated by L5 and S1 in all subjects but in none by the S2 root.

Electrophysiological methods to delineate the segmental motor innervation of the lower limb have been described by Thage (1965) and Phillips and Park (1991). In both these studies ventral roots (L2 – S2 and L1 – S2, respectively) were stimulated in patients undergoing laminectomy; however, Hansen and Schliack (1962) emphasize (p. 33) the difficulty in numerating the lumbosacral spinal roots during laminectomy. Phillips and Park (1991) used bony landmarks or X-rays to identify the individual roots in the subarachnoid space, and are in general agreement with our study stimulating L3 – S1(S2) spinal nerves. The quadriceps muscle was innervated by both the L3 and L4 roots in all (Table 4), and additionally by the L5 in another few subjects as previously reported by Thage (1965, 1974). On the other hand, the anterior tibial muscle was innervated by L5 in 90% of our patients and by the L4 in 70% while Thage (1965) found a higher proportion supplied by L4 than by L5. The peroneus longus, extensor digitorum brevis, biceps femoris and gastrocnemius muscles also showed small differences in root emphasis but the roots contributing to the muscles were similar (Table 4).

In our study the contribution of S2 was only examined in three subjects, making the contribution of this root uncertain. For example, the abductor hallucis muscle was innervated by the S2 in all three instances and in two of these monosegmentally. In another three subjects in whom the S2 contribution was not examined, stimulation of either the L5 or the S1 spinal nerve failed to elicit a response. Monosegmental innervation was, in agreement with Phillips and Park (1991) (*cf* Hansen and Schliack 1962, p. 27), relatively rare being present in three anterior tibial (two L5 and one L4) and one peroneus longus (S1) muscle. One extensor digitorum brevis, one gastrocnemius, and four abductor hallucis muscles were monosegmentally S1 innervated. However, since the S2 root in these muscles makes a contribution, the fact that the S2 was not stimulated in these six cases makes the conclusion regarding the innervation uncertain.

Postfixation of the lumbosacral plexus was noted by Phillips and Park (1991). In our study, two of 10 subjects had CSAPs of about equal amplitude which were recorded at both L4 and L5 spinal nerves during stimulation of the saphenous nerve at medial epicondyle. In these two subjects, stimulation of L4 and L5 spinal nerves evoked CMAPs of the same amplitude in the quadriceps muscle, suggesting a postfixed plexus (i.e. formation of the n. furcalis by the fifth lumbar spinal nerve) which, according to Horwitz's dissections (1939), occur in approximately 15% of the subjects.

Conduction through the lumbosacral plexus

The marked diminution of the amplitude of the CSAP due to temporal dispersion as a function of conduction distance confirmed earlier findings in a small number of normal subjects (Horowitz and Krarup, 1992). In the previous study, recording of the spinal potential was performed only at S1, suggesting that the reduction in amplitude might be due to branching of fibres to different roots. In the present study, the sural nerve was found to project to the L5 and S2 in addition to the S1 root; due to dispersion and phase cancellation, summing of the potentials of the spinal nerves would not be expected to increase the amplitude proportionately to the peak-to-peak amplitudes at the individual roots. However, the dispersion confirms that the amplitude of the CSAP tend to level off at long conduction distances due to the reduction in phase cancellation (Kimura *et al.*, 1988).

As we recorded the CSAP at different sites along the nerve, the conduction velocity was also calculated along the segment across the lumbosacral plexus. The variability of this proximal conduction velocity was somewhat greater than the velocity measured more distally. This variability was probably related to the difficulty of measuring the distance along deep structures from the gluteal crease to the spinal recording electrode. In our calculations we subtracted 30 mm from the distance measured on the skin without taking into consideration individual variations. The conduction velocity along the sural nerve, including the proximal segment across the lumbosacral segment, remained constant, except for the very distal segment from ankle to midcalf. The conduction velocity along the distal part of the nerve was determined between a site of stimulation at the ankle and a site of recording at midcalf, whereas the conduction velocities at more proximal sites were determined between sites of recording. These two methods are not directly comparable due to the influence of a utilization time of 0.15 ms (Krarup *et al.*, 1992). If this stimulus delay is subtracted from the latency, the conduction velocity from ankle to midcalf increased to 56.8±0.8 ms which in the ANOVA test was not significantly different from the more proximal velocities ($P = 0.49$). In contrast to earlier suggestions (Rivner *et al.*, 1990), our electrophysiological findings do not indicate that the diameters of the largest fibres in the nerve taper throughout the length of the nerve except in the most distal part of the limb and support findings by Horowitz and Krarup (1992) and Trojaborg *et al.* (1992). In agreement with other studies a reduction in diameter only occurs distally (Behse, 1990) and is probably related to branching (Berthold, 1978). In view of the uncertainty of distance measurements, the conduction velocity of 55–60 m/s along the sural nerve across the lumbosacral plexus was similar to the conduction velocity of 60–65 m/s along dorsal roots found through spinal recordings of somatosensory evoked potentials (Delbeke *et al.*, 1978).

The amplitudes of gastrocnemius CMAPs evoked by stimulation of individual spinal nerves were markedly smaller than the CMAP evoked by stimulation of the tibial nerve at the popliteal fossa or the sciatic nerve at the gluteal crease. However, the sum of the spinally evoked responses was similar to that evoked at the popliteal fossa and larger than that evoked at the gluteal crease, indicating that the reduction in amplitude was in part due to branching and in part to temporal dispersion. The motor conduction velocity was similar along the thigh and across the plexus, also suggesting that tapering of motor fibres did not occur. The lumbosacral conduction velocities along fibres to the gastrocnemius and to the biceps femoris were similar but greater than the velocity along fibres to the abductor hallucis in agreement with findings by Gassel and Trojaborg (1964). This difference suggests that the fibres to the very distal muscles had a thinner calibre even proximally in the leg than fibres to proximal muscles. The lower distal conduction velocity compared with proximal conduction velocity may be explained by this difference rather than by tapering of nerve fibres.

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DISTAL MOTOR AXONOPATHY AND CENTRAL NERVOUS SYSTEM MYELIN VACUOLATION CAUSED BY CYCLOLEUCINE, AN INHIBITOR OF METHIONINE ADENOSYLTRANSFERASE

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SUMMARY

Cycloleucine (CL), an inhibitor of methionine adenosyltransferase, has previously been used to produce an experimental model of subacute combined degeneration of the spinal cord. A re-investigation of its effects on the morphology of the nervous system and on brain concentrations of methionine and S-adenosylmethionine (SAM) was undertaken.

Cycloleucine was administered as a single dose intraperitoneally (2 mg/g body weight) to young mice aged 21 d and adults aged 6 or 10 wks. The 21-day-old mice showed clinical evidence of toxicity within 24 h and thereafter developed progressive muscle weakness and ataxia. Animals did not survive longer than 1 wk. Light and electron microscopic examination of the central and peripheral nervous systems showed that intramyelinic vacuolation developed in the white matter of brain and cord within 12 h. The intramyelinic vacuolation in the white matter of brain and cord became more severe with longer survival, vacuoles coalescing and secondary axonal degeneration becoming evident. There was no myelin vacuolation in peripheral nerves. Axonal lesions occurred in the distal parts of motor nerves within 12–24 h resulting in degeneration of intramuscular nerve fibres and terminals. Later there was evidence of axonal degeneration in tibial and sciatic nerves. Many dorsal root ganglion cells became vacuolated or necrotic and numerous degenerated fibres were noted in the white matter of the spinal cord, particularly in the gracile funiculus. The optic nerves were not affected at any stage.

In adult mice the pathology consisted of distal motor axonal degeneration which developed at 1–2 d. Little or no intramyelinic vacuolation in white matter was noted.

Brain concentrations of SAM were reduced and levels of methionine became greatly elevated. The morphological effects of CL are considered to be the result of SAM deficiency impairing transmethylation processes known to be important in the formation and stabilization of myelin through the methylation of myelin basic protein. The immature developing central nervous system is much more vulnerable than the fully myelinated adult brain and spinal cord. The distal, predominantly motor axonopathy is a new observation and may be a reflection of the importance of transmethylation processes in the maintenance of axonal terminal membranes and the mechanisms of release of acetylcholine at the neuromuscular junction.

INTRODUCTION

Subacute combined degeneration (SCD) of the spinal cord, described by Russell *et al.* (1900), has long been known to be associated with pernicious anaemia. Although SCD is now treated effectively with vitamin B_{12} its pathogenesis is still not clear. It is widely accepted that in the methyl transfer pathway vitamin B_{12} is a crucial coenzyme of methionine synthetase. Deficiency of vitamin B_{12} leads to failure of transfer of methyl

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groups from methylcobalamin to methionine (Chanarin *et al.*, 1985) resulting in a decrease of S-adenosylmethionine (SAM) levels in the central nervous system (CNS) and thus a failure of transmethylation processes.

A model for the experimental production of SCD was devised by Gandy *et al.* (1973). They used 1-aminocyclopentane-1-carboxylic acid, usually referred to as cycloleucine (CL), which is a synthetic amino acid shown by Lombardini *et al.* (1970) to be a potent inhibitor of methionine adenosyltransferase. Gandy *et al.* (1973) found that administration of CL to mice resulted in white matter changes in the CNS which they considered to have the characteristic features of SCD. Ramsey and Fischer (1978) administered CL to immature rats and observed intramyelinic vacuolation in the white matter of the spinal cord. Small *et al.* (1981) injected large doses of CL into young chickens and noted that the myelinic vacuolation was due to splitting at intraperiod lines.

The published reports of the effects of CL have not included detailed electron microscopy of the white matter of the CNS and, although Nixon (1976) mentioned degeneration in the sciatic nerve, there have been no detailed morphological studies of the peripheral nervous system.

The experiments reported in this paper were carried out to investigate the morphological effects of CL in the central and peripheral nervous systems of the mouse and to compare the changes in the immature young animals with those in adult animals.

It was found that intramyelinic vacuolation developed rapidly in the young animals but in the adults very little vacuolation occurred. No vacuolation was found in peripheral nerve myelin sheaths but a distal motor axonopathy developed within 24 h in both young and adult mice. A preliminary report of these findings was given by Lee *et al.* (1990).

MATERIALS AND METHODS

Animals

More than 100 mice (3–25 wks old), both male and female, were used. Most of them were BALB/c mice but some were from non-inbred strains. There were no differences detected in the experimental results which might be attributable to the differences in sex or strain. They were caged in groups of three to seven and were fed on solid pellets (CRM diet-Labsure) and tap water *ad libitum*. The food pellets were soaked in tap water and spread on the floor of cage to facilitate feeding and access by behaviourally affected mice.

Cycloleucine (CL) (Sigma) was used in freshly made solution of 500 mg in 10 ml sterile distilled water.

Experiments

Mice were given CL (2 mg/g) intraperitoneally in a single dose. These animals were divided into two major groups, 21 young mice aged 21 d and 41 adults aged 6–10 wks. The young animals were allowed to survive from 12 h to 7 d. Several animals, not included in these studies, died before 7 d and none survived longer than 7 d. The adult animals were allowed to survive from 1 d to 14 d.

Controls included 16 BALB/c mice, aged 3–25 wks, which received an intraperitoneal injection of 0.4–1 ml distilled water. They were allowed to survive up to 13 d. In addition, four normal mice were killed by perfusion for electron microscopy.

Histology and electron microscopy

The mice were perfused through the left ventricle with fixative under anaesthesia. For paraffin histology the fixatives used were formol-calcium (10% formalin in 1% calcium acetate) followed by formaldehyde-glacial acetic acid-methanol. After overnight fixation mice were decalcified in formic-citrate solution and blocks taken to include head, trunk and limbs. Sections were stained with haematoxylin-eosin, haematoxylin-van Gieson, luxol fast blue-cresyl violet and silver impregnation for axons (Marsland *et al.*, 1954). For electron microscopy mice were perfused with 40 ml cold freshly prepared glutaraldehyde-paraformaldehyde in cacodylate buffer (Karnovsky, 1965). Transverse cuts were made across cervical and lumbar spine to facilitate penetration of fixative. After overnight fixation blocks were taken from many regions of brain and spinal cord, peripheral nerves and muscles, post-fixed in osmium tetroxide, dehydrated and embedded in araldite. Sections cut at 1 μm were stained with toluidine blue and ultrathin sections stained with uranyl acetate-lead citrate and examined at an accelerating voltage of 80 kV.

Biochemistry

In order to confirm that CL inhibited methionine adenosyltransferase, brain concentrations of methionine and SAM were determined at times up to 5 d after administration of CL in 21-day-old mice. Methionine and SAM were measured by high-performance liquid chromatography (Surtees and Hyland, 1989, 1990). The brain was removed within 1 min of death and frozen immediately in liquid nitrogen. As soon as possible afterwards the brain was thawed, homogenized and deproteinized prior to the assay.

RESULTS

Twenty-one-day-old mice

Clinical observations

The mice were assessed clinically before and immediately after the intraperitoneal injection of CL and then checked twice daily. Motor function was assessed by placing the mouse on a wire grid with squares of approximately 2 cm, the animal's ability to walk, climb and grip the wire with its paws being noted. Sensation was tested by lightly pinching the tail and the feet and observing the presence or absence of a withdrawal response.

Normal control mice

The control mice were active and showed no signs of muscle weakness at any time. When placed on the wire grid, they were able to grip the wire firmly with all four feet, and walked rapidly, hardly ever losing their footing. When lifted by the tail, they would extend the hind limbs fully and straight, with the toes of each foot widely spread. If lifted from the wire grid the mouse normally grips the wire firmly by the fore paws.

Cycloleucine-treated mice

Mice looked normal and active immediately after the injection. At 12 h there was no sign of motor or sensory dysfunction. At 24 h mice were obviously ill and had a staring ruffled coat. They showed weakness of the hind feet but there was no weakness of fore legs and no apparent disturbance of sensation. By 36 h mice were ataxic and there was marked weakness of the hind legs and feet. When lifted by tail, they did not extend the limbs fully or spread the toes. When placed on a wire grid, the hind feet could not grip the bars though the fore paws could do so. At 48 h after the injection, the animals looked very ill and loss of body weight was apparent and by 72 h some had died. The surviving mice showed severe weakness in hind limbs and almost complete paralysis of the foot muscles. Misplacement and dragging of hind limbs were noted in most mice and, when placed on a wire grid, they could hold the bars only with the fore paws. Sensation seemed to be intact. There was also paralysis of abdominal and respiratory muscles, and costal recession was apparent. These signs were progressive and none of the 21-day-old CL-treated mice survived long than 7 d.

Morphological observations

Central nervous system

Twelve hours. Vacuolar changes in the white matter of the cerebellum and spinal cord were present, the vacuoles mostly having the shape of a crescent partly enclosing the axon. The distribution of vacuoles was uneven. In the cerebellum the fibres in the folia were more affected than deep white matter and in the cervical spinal cord the dorsal columns were more affected than lateral or ventral white matter. In the thoracic cord only dorsal columns showed vacuolation. No vacuolation was visible in the molecular or granular layers of cerebellum and neurons of the cerebellum and spinal cord were of normal appearance. Optic nerves appeared within normal limits, no vacuolated fibres being detected in them at this or at any stage.

With electron microscopy it was clearly seen that the vacuolation was intramyelinic and the result of splitting at the intraperiod line (Figs 1, 2). In some fibres there seemed to be several splits in the myelin sheath. Affected fibres were mostly of the order of $1-2$ μm diameter. The vacuoles appeared to be empty; presumably their contents had been removed during processing. The axons of fibres showing myelin vacuolation did not appear abnormal. Axonal microtubules and filaments, mitochondria and cisternae

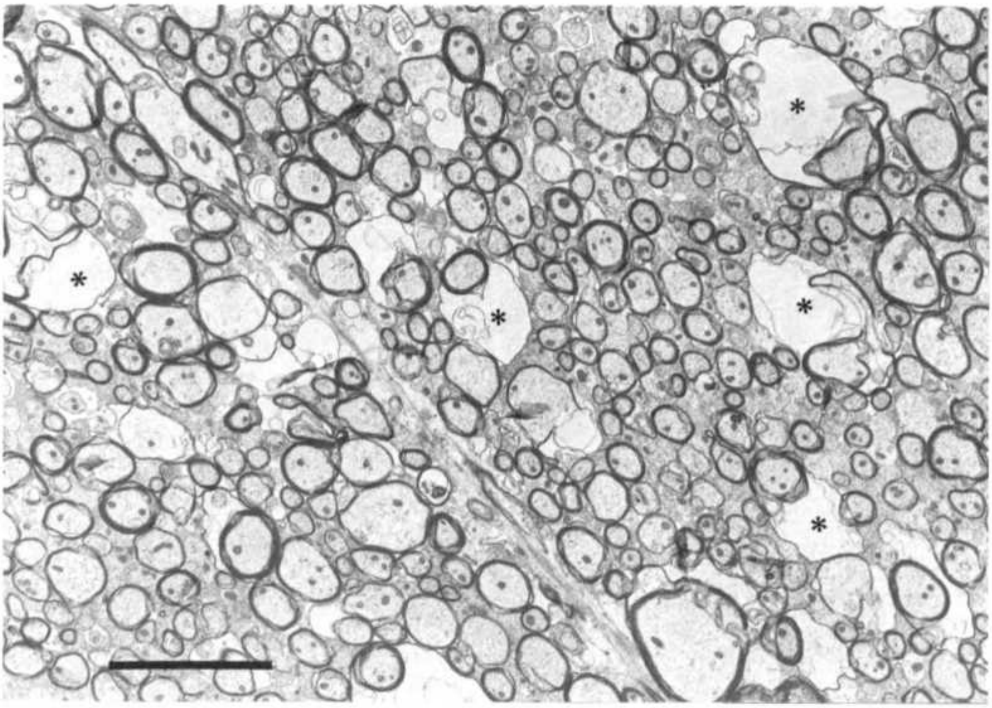

FIG. 1. Electron micrograph of dorsal column of young mouse 12 h after administration of CL. Intramyelinic vacuoles (asterisks) are already present. Bar = 5 μm.

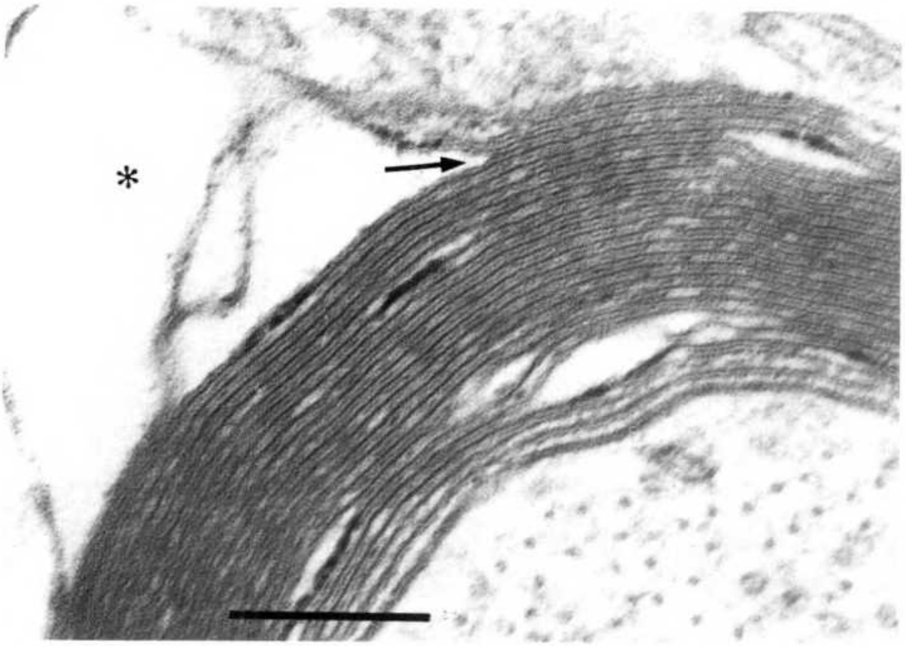

FIG. 2. The vacuole (asterisk) in the myelin sheath has been formed by the splitting of myelin lamellae at an intraperiod line (arrow). Bar = 0.2 μm.

of smooth endoplasmic reticulum all appeared to be within normal limits. Oligodendrocytes did not show degenerative changes or vacuolation. Neurons in cerebellum and in spinal cord as well as axonal terminals, dendritic profiles and synapses showed no abnormalities.

Twenty-four hours. Vacuolation of the white matter was fairly generalized affecting cerebral as well as cerebellar tissue. Deep as well as foliar white matter showed intramyelinic vacuolation which was now also more widely distributed in ventral and lateral as well as dorsal columns of the spinal cord. Fibres of all sizes seemed to be affected.

With electron microscopy the vacuoles could be seen to vary in size. Most were rounded rather than crescentic and many were multiloculated (Fig. 3) and several times the diameter of the axon with which they were associated. Neurons, synapses and oligodendrocytes were normal in appearance and there was no sign of axonal or nerve fibre degeneration.

Forty-eight hours. The vacuolation of white matter in the cerebral hemispheres and in the cerebellum was now very severe. The tissue had a diffusely spongy appearance and only in some small areas were myelinated fibres spared. Vacuoles were mostly rounded and large, three or four times the diameter of the axons. Some myelin lamellae could be seen immediately surrounding the axon. The vacuoles were multilocular, traversed by lamellae of myelin. Oligodendrocytes were of normal appearance. In the dorsal columns of the spinal cord there was an occasional degenerating nerve fibre.

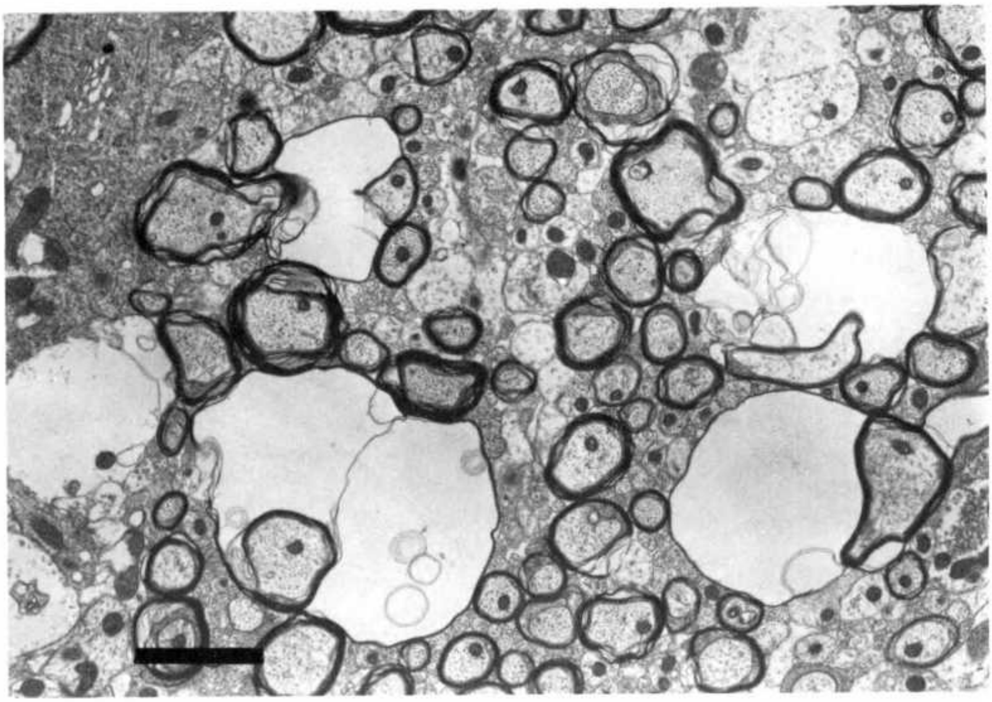

FIG. 3. Lumbar spinal anterolateral white matter 24 h after CL administration. Vacuoles are rounded and multilocular and bounded by a few lamellae of myelin. Bar = 2 μm.

Seventy-two hours. There was considerable variation among the animals studied in the degree of severity of the myelin vacuolation. In the most severely affected animal the white matter in all regions examined was almost spongy in appearance. Other animals were less severely affected, though even in these there was variation from one site to another. The cerebellum always showed some degree of white matter vacuolation. Some degenerating fibres were present in fasciculus gracilis at cervical level in all mice studied at this time. In the 1 μm sections of spinal cord some vacuolated fibres were seen cut longitudinally (Fig. 4). Here it could be seen that the vacuoles were clearly separated from each other in the long axis of the fibre. It could not be seen whether any vacuoles extended the full length of the internode.

Electron microscopy of ultrathin sections was confined to the most severely affected animal. The vacuoles were large, irregular in shape and coalescent in places with membranes apparently beginning to break down (Fig. 5). Vacuoles which were not enclosed within a clearly defined membrane were quite numerous. Whether this breaking down of limiting membranes was artefactual or not is not certain, but the numbers of these non-bounded spaces lying between identifiable profiles in well-fixed areas indicated a real pathological change. Some axons appeared abnormal in that they were filled with closely packed neurofilaments.

Four days (ninety-six hours). Severe vacuolation in the cerebral hemispheres and of the caudate-putamen and thalamus was present. The cerebellum, pons and medulla were

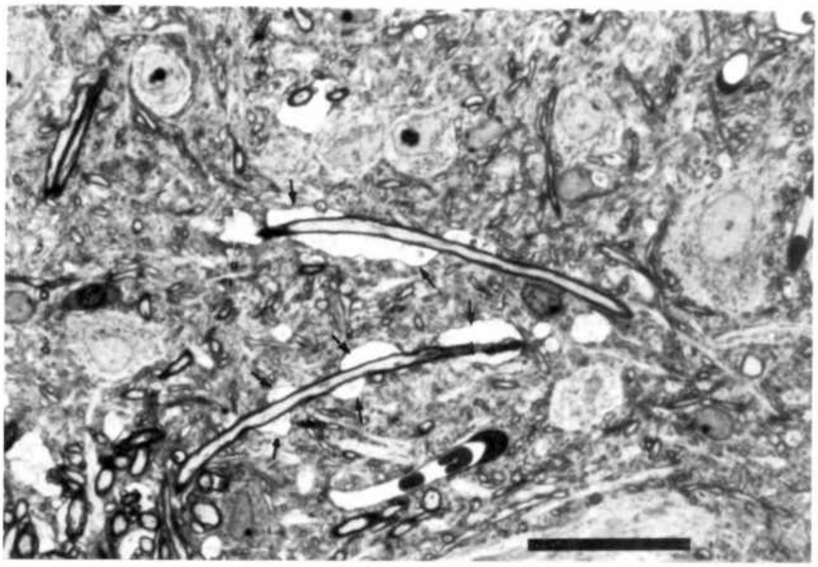

FIG. 4. Sacral spinal cord 72 h after CL administration. Vacuoles (arrows) of varying length lie along two longitudinally sectioned myelinated nerve fibres with normal looking myelin between them. 1 μm plastic section. Toluidine blue. Bar = 50 μm.

also severely affected but the cervical cord showed less marked vacuolation which was mainly present in the corticospinal part of the dorsal column and in deeper parts around the grey matter. The lumbo-sacral cord, however, was very severely vacuolated. At cervical level there were scattered degenerating fibres in the white matter, more numerous in the dorsal columns.

Electron microscopy showed that the vacuoles were irregular in shape and seemed to be confluent and multilocular. Loose membranes were common and some were breaking down. There was evidence of axonal degeneration now taking place, some myelinated axons containing dense bodies and aggregates of tubules.

Five and seven days. Vacuolation of white matter was widespread throughout the CNS. Of interest was vacuolation in the optic tracts but not in the optic nerves. In CNS white matter there were many large irregular spaces lying extracellularly. These contained amorphous granular material or seemed otherwise empty and were probably derived from broken-down vacuoles that were originally intramyelinic. In addition, there were degenerating axons and other degenerative profiles. Nerve cells in brain stem, cerebellum and spinal cord did not look abnormal. There did not seem to be excessive numbers of astrocytes or glial fibres.

Peripheral nerve and muscle

Twelve hours. No evidence of axonal or myelin sheath abnormality was seen in nerve roots, sensory ganglion cells or peripheral nerves by light microscopy or electron microscopy.

Motor end-plates were examined in foot muscles. Axonal terminals were intact and contained abundant clear as well as coated vesicles. Mitochondria looked normal. In

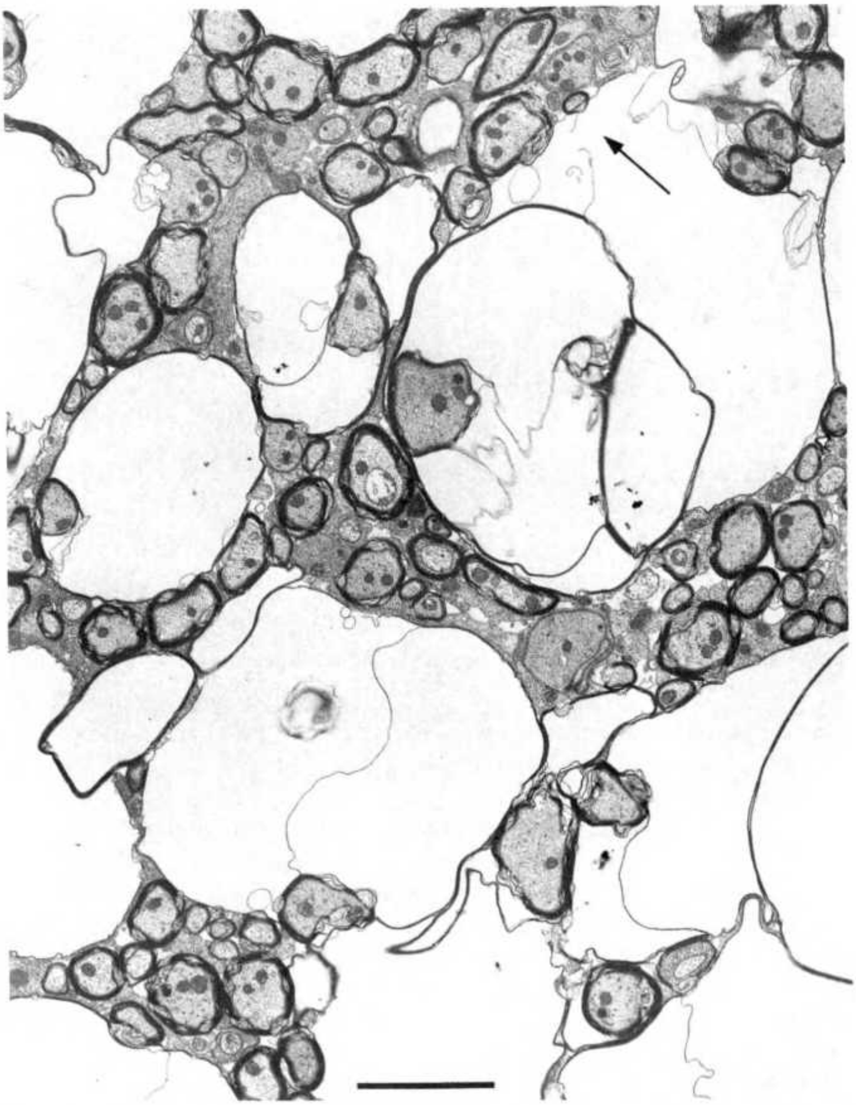

FIG. 5. Cerebellar white matter 72 h after administration of CL. There is severe vacuolation with vacuoles become confluent and the lamellae of myelin are beginning to break down (arrow). Bar = 3 μm.

some end-plates there were electron-lucent distended cisternae or some rarefaction of the axoplasm (Fig. 6). These did not appear to be artefactual and in view of later events may represent very early significant pathological changes.

Twenty-four hours. Paraffin sections of the hind legs and feet were examined with various histological staining methods including silver impregnation. In these sections the intramuscular nerves were well visualized and a varied picture was seen. The larger nerves such as posterior tibial and some of the intramuscular nerve bundles were of

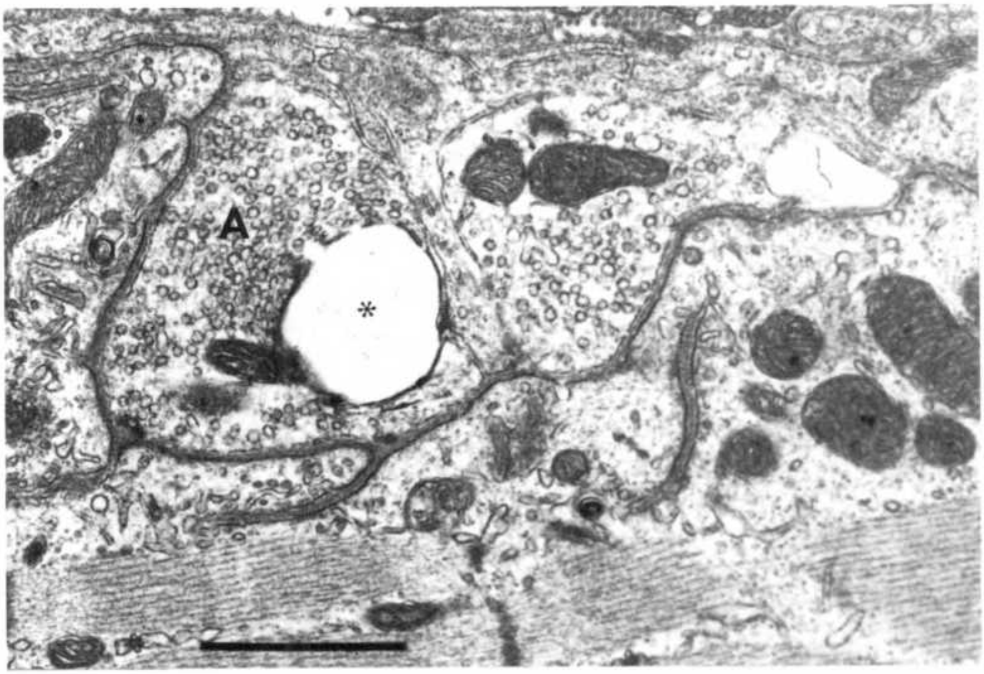

FIG. 6. A motor end-plate of a foot muscle at 12 h. Vacuoles (asterisk) in or close to axonal terminals (A) may be an early sign of degeneration. Bar = 1 μm.

normal appearance. However, there was also evidence of axonal degeneration in some small intramuscular nerves and end-plates. In some small nerves only an occasional axon was present or none at all, and the presence of argyrophilic granules either within the nerve sheath or at the end-plate was evidence of axonal fragmentation.

The sensory innervation of the skin of the foot and toes was seen in abundance and did not show evidence of axonal degeneration.

Ultrathin sections were examined of foot muscles, soleus, extensor digitorum longus (EDL) and posterior tibial and sciatic nerves. In the muscles a total of 16 motor end-plates were studied. Of these one could be described as normal and two were questionably within normal limits, their terminals containing patches of electron lucent axoplasm or dilated membrane-bound cisternae which can sometimes be seen in control material. All the other end-plates showed evidence of abnormality. In some (Fig. 7A) the axonal terminals were rarefied and contained few vesicles in an electron-lucent axoplasm in which mitochondria were swollen and rounded. Processes of Schwann cell cytoplasm interposed between axon terminal and postsynaptic surface of the muscle fibre where they are not normally seen. In other end-plates some axonal terminals looked normal whilst some were degenerating (Fig. 7B). At this stage there were no completely denervated end-plates. Muscle fibres showed no significant changes.

The ultrastructural appearance of lumbar motor and sensory roots, sciatic and posterior tibial nerve were within normal limits. In the smaller distal nerves, however, there were abnormalities in the axons of the intramuscular nerve bundles and in preterminal

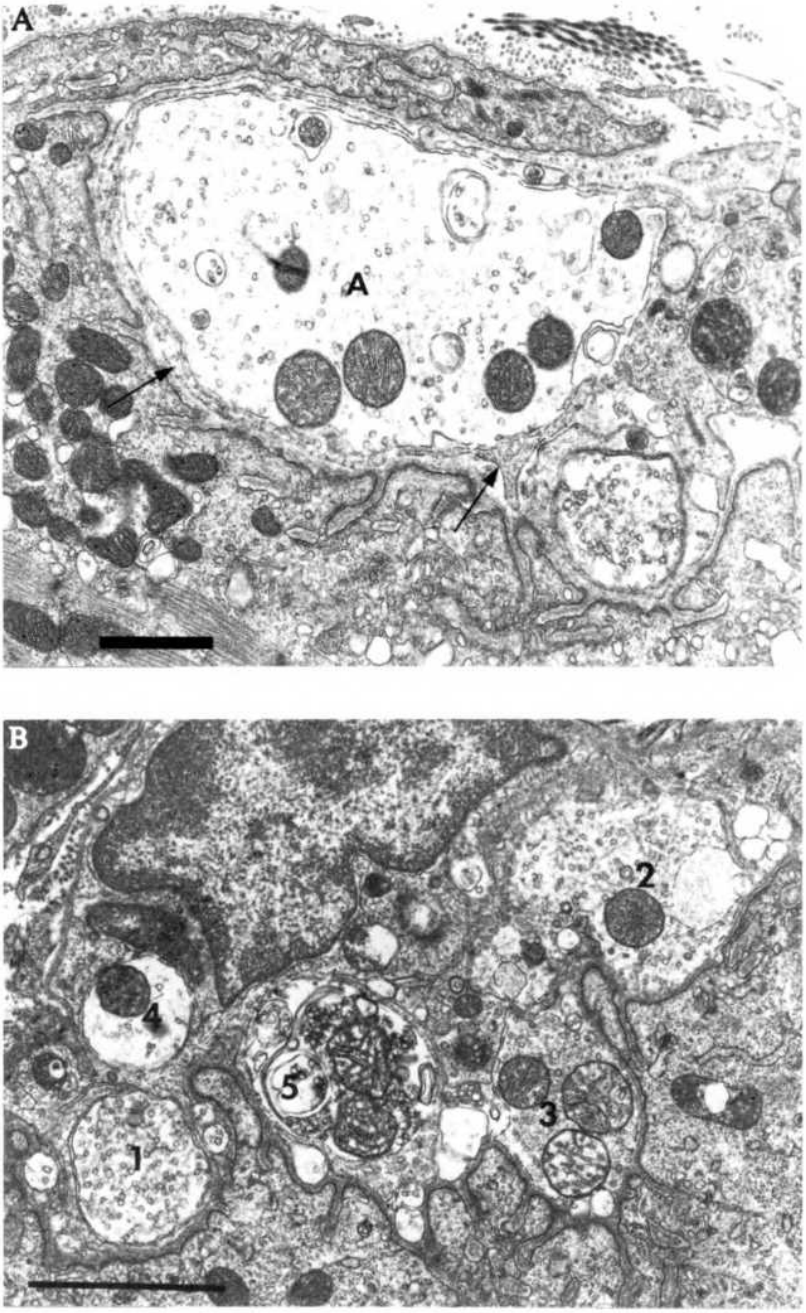

FIG. 7. A, a motor end-plate in a foot muscle 24 h after administration of CL. The electron-lucent axoplasm (A) contains few synaptic vesicles. Mitochondria are rounded and cristae breaking up. Processes of Schwann cell cytoplasm (arrows) enclose the degenerating terminal. Bar = 1 μm. B, end-plate in soleus 24 h after administration of CL with axonal terminals which range in appearance from almost normal (1) to severely degenerated (5). Terminals 2 and 3 show earlier abnormalities including vacuolation and rounded mitochondria and the axoplasm of 4 is rarefied and depleted of vesicles. Bar = 2 μm.

myelinated axons of soleus and foot muscles (Fig. 8) taking the form of rarefaction of the axoplasm or development of membrane-bound vacuoles.

The distal axonal abnormalities were more marked at 48 h. Many nerve fibres lacked axons, only myelin ovoids or irregular dense fragments remaining. In other fibres the axoplasm was electron lucent and contained vacuoles or membrane-bound cisternae, the axonal microtubules and filaments seemed to have disintegrated and mitochondria were rounded and abnormally dense.

A striking contrast was observed between motor nerves innervating extrafusal muscle fibres and those innervating muscle spindles. Extrafusal nerves were severely degenerated whilst the intrafusal myelinated fibres were normal in appearance. In keeping with this observation was the absence of pathological changes in the sensory innervation of intrafusal fibres, the annulospiral endings looking normal.

Fifteen motor end-plates were visualized in foot muscle, soleus and EDL. In the foot muscles, all 10 end-plates seen were denervated and Schwann cell cytoplasm covered

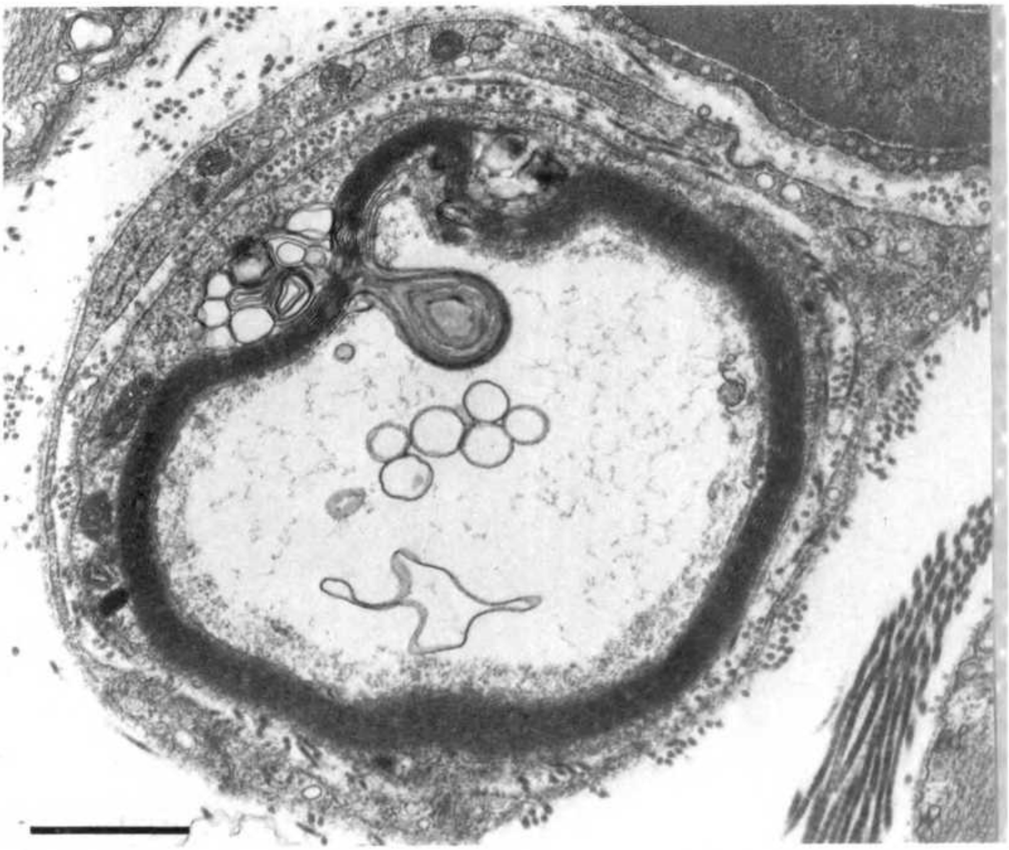

FIG. 8. Myelinated preterminal axon in foot muscle 24 h after administration of CL. The axoplasm is rarefied and does not contain normal organelles. Abnormal vacuoles and amorphous granular material are present and the axolemmal membrane may be breaking down. Bar = 1 μm.

the postsynaptic membrane. In EDL two end-plates were seen and both were denervated while in soleus two end-plates were innervated by normal looking axonal terminals and one was denervated. It seems that the more distal, the more severe and complete the motor neuropathy.

Seventy-two hours. In addition to the distal motor axonopathy causing denervation of all the end-plates observed in foot muscles, soleus and EDL, there were now abnormalities in dorsal root ganglion cells. Many of these neurons were shrunken and it could be seen by electron microscopy that the small densely blue-stained cells were also markedly electron dense (Fig. 9), being packed with laminated or concentrically

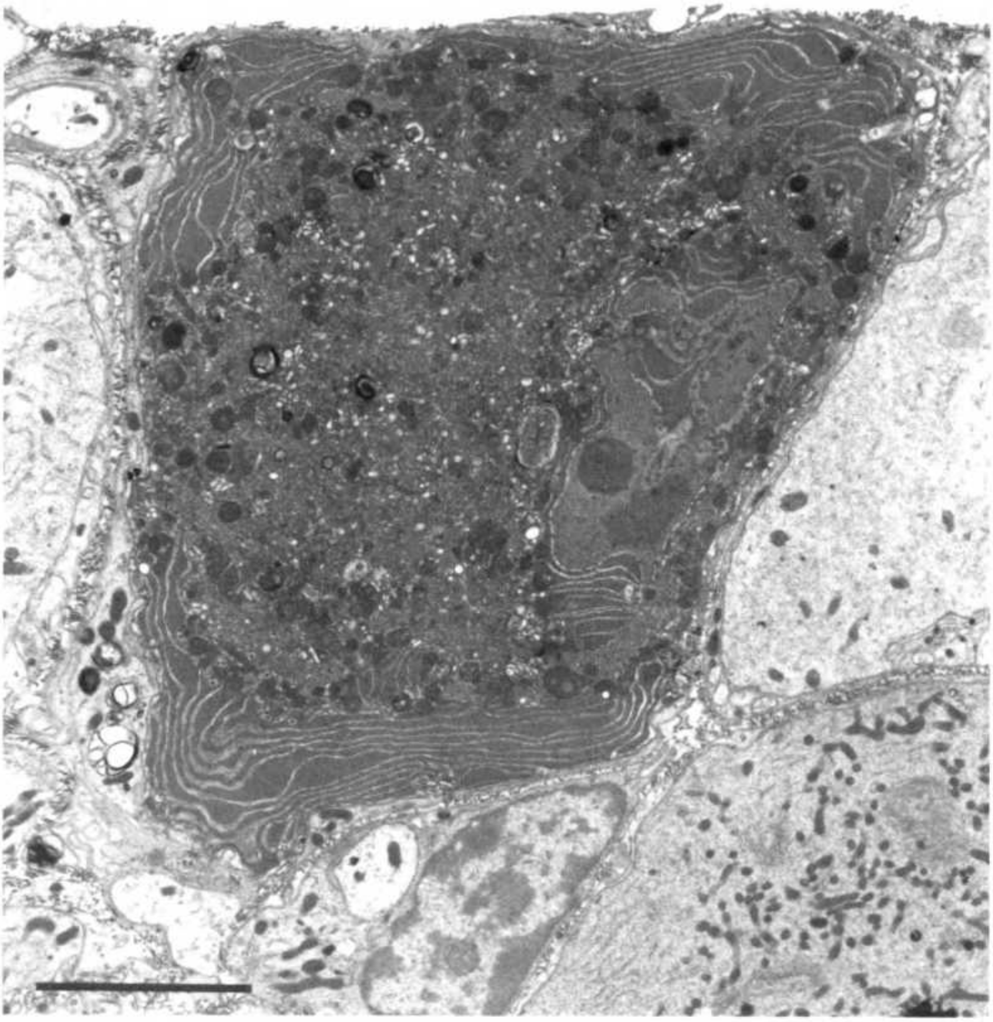

FIG. 9. Necrotic neuron of dorsal root ganglion 72 h after administration of CL. This electron dense cell contains layers of endoplasmic reticulum, dense bodies and degenerated organelles. Bar = 3 μm.

arranged layers of degenerated rough endoplasmic reticulum together with dense aggregates of ribosomes, dense bodies, membranous bodies, vesicles and degenerating mitochondria. About 10% of neurons showed this type of degeneration. Another type of degenerating neuron consisted of replacement of the perikaryon by masses of vesicles, multivesicular bodies, dense bodies and amorphous granular material. Some of this material extended into axonal processes.

Silver impregnation of paraffin sections of the limbs showed a contrast between fore and hind limbs in respect of the state of innervation of their muscles. In the fore limbs there was little or no evidence of axonal degeneration. In the hind limb muscles, however, only larger nerve bundles contained intact axons. There was extensive axonal fragmentation in small intramuscular nerves and in preterminal fibres and almost no intact terminal arborizations were seen. Innervation of spindles seemed to be within normal limits, annulospinal endings being preserved.

Ninety-six hours. All end-plates visualized in soleus and in foot muscles were denervated (Fig. 10). Processes of Schwann cell cytoplasm, some containing fragments of debris, lay in contact with postsynaptic membrane.

Of peripheral nerves studied by electron microscopy the smaller intramuscular nerves showed the most severe abnormalities. Small nerves in soleus, EDL and foot muscles

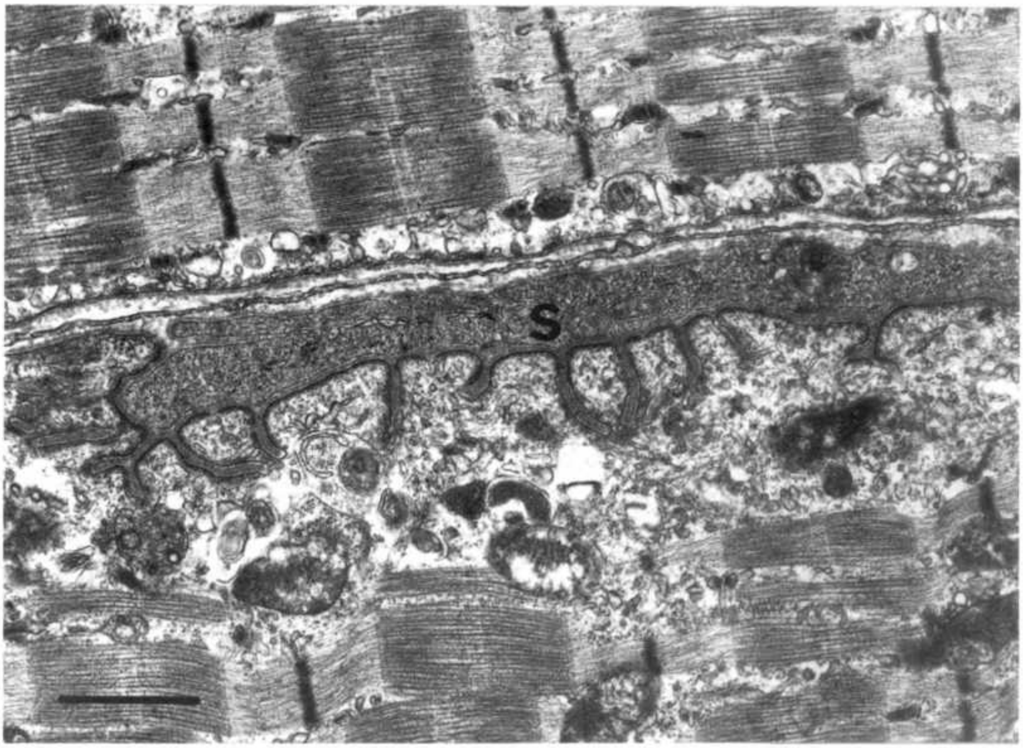

FIG. 10. An end-plate in foot muscle 4 d after administration of CL lacks an axonal terminal. The post-synaptic membrane is covered by Schwann cell cytoplasm (S). Bar = 1 μm.

were almost totally degenerated, whereas intramuscular nerves in the fore limb were of normal appearance (Fig. 11). In larger nerves such as plantar or posterior tibial or sciatic, occasional fibres showed axonal degeneration. No vacuolar or degenerative changes were noted in the motor roots.

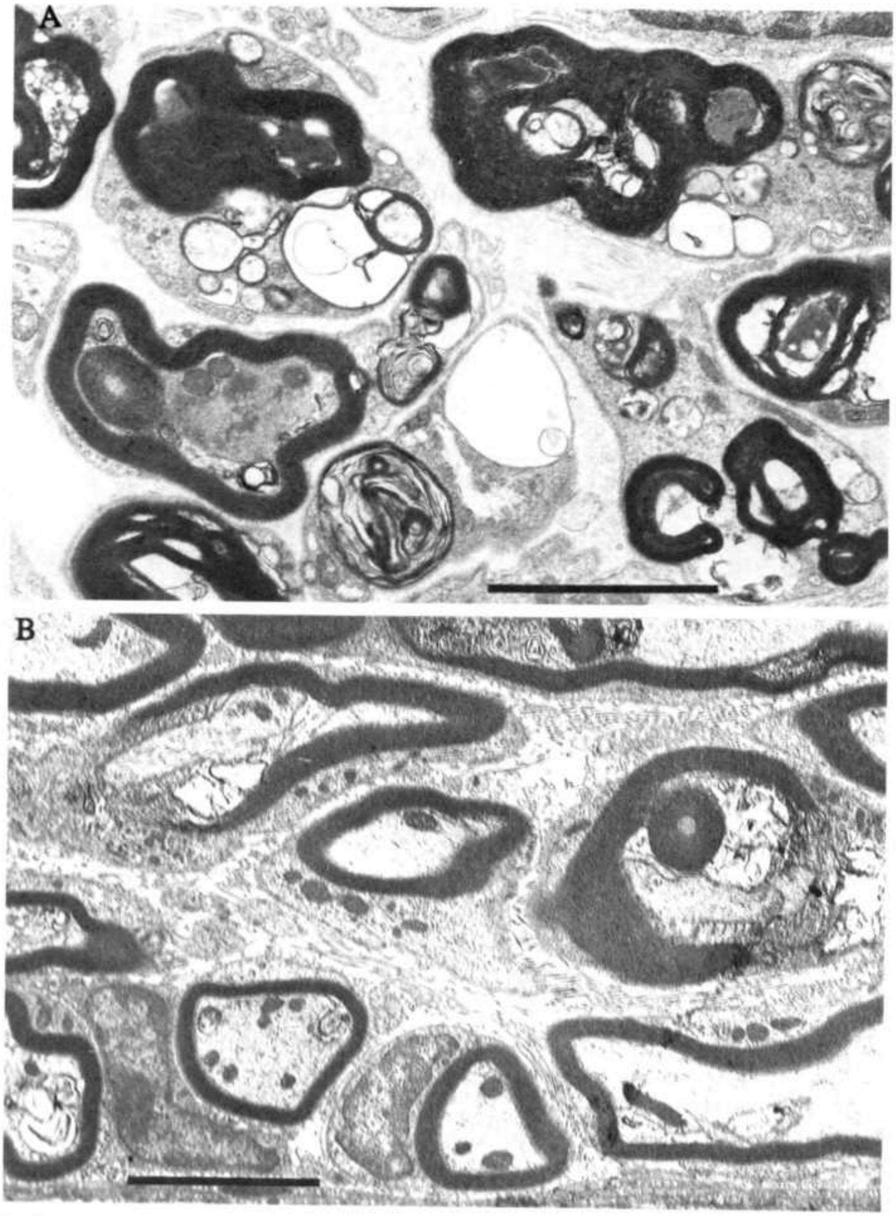

FIG. 11. Intramuscular nerve from a muscle of the hind foot (A) 4 d after administration of CL shows degeneration of every myelinated fibre, in contrast with proximal nerve in biceps brachii (B) which is relatively normal in appearance. Bar = 3 μm.

Dorsal root ganglia contained necrotic neurons. In one lumbar dorsal root ganglion approximately 300 neurons were counted in one section. Of these there were 12 shrunken darkly stained cells.

Five to seven days. During this time the main addition to the pathological changes now observed involved the larger peripheral nerves (Fig. 12). In the sciatic and tibial nerves there were many fibres which showed varying degrees of fragmentation of myelin around a central space devoid of axon. Debris lay within the cytoplasm of Schwann cells. Although a few unmyelinated axons contained dense bodies or whorls of membrane there was no convincing evidence of degeneration of these unmyelinated fibres. The striking contrast between the fore limb muscle biceps brachii and the muscles of the leg and foot was maintained. In biceps brachii intramuscular nerves and end-plates were of normal appearance. In soleus, EDL and foot muscles intramuscular nerve branches showed severe, almost total degeneration and every end-plate identified was denervated.

Adult (six- and ten-week-old) mice

Clinical observations

Although there was some variation in the severity of effects of CL from one animal to another, in general, they were similar to, but developed more slowly than, those

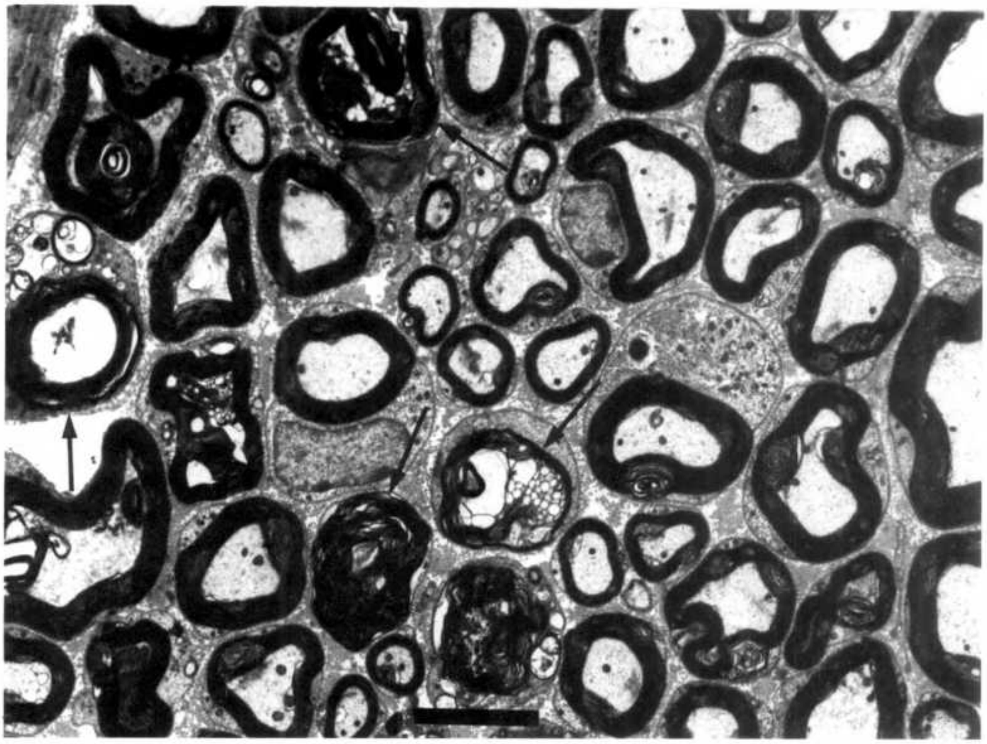

FIG. 12. Sciatic nerve of mid-thigh level at 4 d after administration of CL. Fibres in varying stages of axonal degeneration are shown (arrows). Bars = 3 μm.

of 21-day-old mice. Animals looked normal and active immediately after the injection. At 24 h they showed few signs of neurotoxicity and there was no motor or sensory abnormality. At 48 h they were obviously ill and showed weakness of the hind feet. There was no weakness of fore legs and no apparent disturbance of sensation. By 3 d there was clearly weakness of the hind legs and hind feet.

By 4 d after the injection, gait was severely ataxic, there was paralysis of abdominal and respiratory muscles, and costal recession was apparent. By 5 d they showed more severe weakness of hind limbs and almost complete paralysis of the foot muscles. After 7 d the severe weakness of hind limbs persisted and became almost total by 10 d. Animals were allowed to survive for up to 14 d.

Morphological observations

Central nervous system. In the 6-wk-old mice there were very occasional vacuoles in the spinal white matter by 24 h. The severity of vacuolation was much less than those of 21-day-old mice. By 48 h there were more vacuoles in the cerebellum but very few in the spinal white matter and by 3 d, the vacuolation in cerebellar white matter was slight more prominent in the 6-wk-old mice but was not seen in the spinal white matter. At 6 d there were more numerous vacuoles in the cerebellar white matter but very few in the spinal cord in the 6-wk-old mice. In the 10-wk-old mice no intramyelinic vacuolation could be found in the CNS at any stage. Only 10-wk-old animals survived more than 6 d. After that time there were many degenerated myelinated fibres in the dorsal columns and also occasional degenerated fibres scattered in the rest of the spinal white matter. Nerve cells in the spinal cord appeared normal, but dorsal root ganglion cells were not studied in these animals.

Peripheral nervous system. At 24 h most axonal terminals and nerve fibres in the muscles appeared normal or very slightly affected. An occasional intramuscular fibre showed axonal rarefaction. By 48 h many intramuscular nerve fibres contained severely degenerated axons. In some of them the axons appeared electron dense and some showed rarefaction of the axoplasm. The myelin sheaths showed only slight changes. The muscle fibres were normal.

By 3 d the peripheral nerves showed severe distal axonopathy without intramyelinic vacuolation. As in the young animals the distal intramuscular hind limb motor nerves and axonal terminals were affected, those in the muscles of head, trunk, fore limbs and proximal part of hind limbs appeared normal. Muscle spindles and the innervation of the skin appeared normal. The distal motor axonopathy became progressively more severe and extensive until day 9–10. After that it did not appear to progress and at 14 d there were some end-plates with small axonal terminals packed with vesicles suggesting that there may have been a beginning of axonal regeneration. The animals, however, were by that time severely ill and could not survive longer than 14 d.

Biochemistry

The results are shown in Fig. 13. The concentration of SAM in the brain of normal mice was 34 nmol/g (mean of three animals). Within 24 h, the concentration had fallen to 21 nmol/g and by day 5 to 17 nmol/g. Thus there was a rapid decline in SAM levels to 60% of normal within the first 24 h after the administration of CL. Simultaneously, brain levels of methionine rose from 38 nmol/g in the normal group to 447 nmol/g at

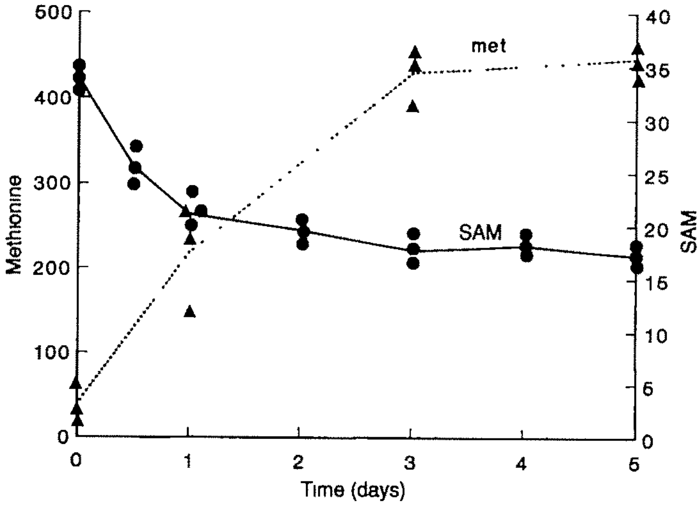

FIG. 13. Effect of CL on brain concentrations (in nmol/g wet weight) of SAM (●) and methionine (▲). Levels of SAM fell to 60% of normal within 24 h. Methionine levels increased more than tenfold in 5 d, the result of inhibition of methionine adenosyltransferase.

5 d a rise of more than tenfold. These changes indicate marked inhibition of methionine adenosyltransferase.

DISCUSSION

Cycloleucine was first used to produce an experimental model for SCD of the cord in mice by Gandy *et al.* (1973) but no ultrastructural studies were reported. Ramsey and Fischer (1978) reported the splitting of myelin sheaths in immature rats. Small *et al.* (1981) injected a large dose of CL into chicks and found clear vacuoles in the myelin sheaths in the brain; they also reported a 50% decrease of myelin basic protein and a 50% inhibition of methylation of arginine in the myelin protein.

In addition to the intramyelinic vacuolation and demyelination previously reported, we have observed distal motor axonopathy and necrosis of dorsal root ganglion cells. These, to our knowledge, have not been described before as an effect of CL. The intramyelinic vacuolation affected only the central but not the peripheral nervous system and it occurred in young developing mice and not in the older mature mice. This suggests that the different components of myelin in the central and peripheral nervous systems and also the differences in the composition of myelin at different ages may play an important role in the formation of intramyelinic vacuoles.

Two hypotheses have been proposed to explain how CL affects the myelin sheath. One, by Jacobson *et al.* (1973), is that CL is a competitive inhibitor of methionine adenosyltransferase, which converts methionine to SAM, a donor of methyl groups for numerous transmethylation reactions. Jacobson *et al.* (1973) proposed that CL causes degeneration of myelin by inhibiting the methylation of phosphatidylethanolamine leading to a decline in the levels of phosphatidylcholine which is an essential component of myelin. The other hypothesis was proposed by Small *et al.* (1981) who thought that the inhibition of methylation of myelin basic protein (MBP) might be responsible. Myelin basic protein is a major protein in CNS (30–40% of myelin protein) and only a minor component of peripheral nerves (18% of myelin protein). As MBP has been shown to cross-link lipid vesicles, it may stabilize the compaction of myelin by cross-linking the lamellae in a similar fashion. Myelin basic protein is thought not to be as important for maintaining the compaction of myelin in the PNS as in the CNS (Kirschner and Ganser, 1980). Myelin basic protein can be methylated at a single arginine residue by the enzyme, protein methylase 1, using SAM as substrate producing two forms of methylated MBP: one, with monomethylarginine and the other with dimethylarginine. A third form, MBP-unmethylated is also found. Methylated arginine might play a role in stabilizing the conformation of MBP by cross-chain reactions, since methylated arginine is more hydrophobic than arginine itself (Brostoff and Eylar, 1971). Cycloleucine strongly depresses methyl incorporation into arginine *in vivo* (Small *et al.*, 1981), indicating that methylation of MBP could be inhibited.

DesJardins and Morell (1983) studied the comparison of phosphorylation and methylation of basic protein *in vivo* during development. They found the rate of methylation of MBP slowed with development and appeared to be proportional to the rate of synthesis of MBP. This suggested that methylation occurs only as MBP is being synthesized and that MBP molecules previously assembled into myelin were no longer available for methylation. The level of MBP in whole brain increases as the rate of myelination increases (Campagnoni *et al.*, 1978; Benjamins, 1984). Analysis of the rates of synthesis of the 14K and 18.5K MBP in mouse brain between 14 d and 39 d showed a peak of synthesis of both proteins at 18 d of age, coincident with the period of maximal myelin deposition. This may explain why CL caused intramyelinic vacuolation in the CNS white matter in young developing mice but not in older mature mice.

Vitamin B_{12} is a corrin ring-containing co-enzyme which is required for normal growth and development of the nervous system. There are only two vitamin B_{12}-requiring enzymes which have been identified in mammalian systems. They are methionine synthetase, which regenerates methionine from homocysteine, and methylmalonyl CoA mutase, which converts methylmalonyl CoA to succinyl-CoA. It has been suggested previously that the pathogenesis of SCD is caused by the failure of transfer of methyl groups from methyl-cobalamin to homocysteine for the regeneration of methionine via methionine synthetase. Scott *et al.* (1981) treated monkeys with nitrous oxide, which is known to inactivate vitamin B_{12}, and produced SCD. Simultaneous supplementation of methionine in the diet significantly ameliorated the nitrous oxide-induced lesion in the monkeys. Scott *et al.* (1981) suggested that the root cause of SCD was likely to be the inhibition of vitamin B_{12}-dependent enzyme methionine synthetase not the inhibition of methylmalonyl CoA mutase. Van der Westhuyzen *et al.* (1982) administered nitrous oxide to fruit bats causing SCD. They found that supplementing the diet with methionine was protective. They suggested that these findings would lend support to the hypothesis that the neurological lesion in vitamin B_{12} deficiency may be related to the deficiency in the methyl donor SAM.

In the parallel biochemical study of CL-treated mice, concentrations of methionine and SAM were measured in brain from the day of injection to 5 d afterwards. The brain levels of SAM fell to approximately 60% within 1 d and to approximately 50% of normal at 5 d. The brain levels of methionine underwent a marked increase within 1 d and tenfold increase by 5 d. These results show that CL is an inhibitor of methionine adenosyltransferase which leads to a significant fall of SAM levels in the CNS. The transmethylation of the arginine 107 residue in MBP has been proposed by Small *et al.* (1981) to be essential for maintaining the compaction of the myelin sheath. In the immature CL-treated mice the intramyelinic vacuolation may be caused by the failure of methylation of MBP in the arginine residue 107 due to SAM deficiency. In the adult mice, the reason why there was no intramyelinic vacuolation may be because most MBP has already been methylated.

The exact mechanism of separation of myelin lamellae is still unknown. The conditions which are known to cause splitting of myelin sheaths in the central and peripheral nervous system were reviewed by Agamanolis *et al.* (1978). Compounds which are known to produce vacuolation in the CNS include hexachlorophene (HCP), triethyl tin (TET), isoniazid (INH) and cuprizone.

Hexachlorophene causes intramyelinic vacuolation in peripheral nerves as well as CNS (Towfighi *et al.*, 1973). The mechanism of intramyelinic vacuolation caused by HCP is still unclear. Within 1–2 h of intravenous injection of TET in the rat, Jacobs *et al.* (1977) found that intramyelinic vacuoles appeared with no accompanying or preceding changes in astrocytes or oligodendrocytes. No effects were found in peripheral myelin. Blakemore (1980), summarizing the findings in the CNS in experimental INH intoxication, noted that intramyelinic vacuolation developed in chicks, ducklings and dogs. The vacuoles arose at the intraperiod lines. Distal axonal degeneration, affecting motor fibres more severely than sensory, was found by Cavanagh (1967) and confirmed by Jacobs *et al.* (1979). Cuprizone causes intramyelinic vacuolation with separation at intraperiod lines (Suzuki and Kikkawa, 1969). Blakemore (1972) considered that cuprizone acted directly upon myelin-forming oligodendrocytes since degenerate oligodendrocytes were found in cuprizone-treated mice at all stages of intoxication. Love (1988) observed that cuprizone induced intramyelinic vacuolation but not demyelination in the rat. He also found that cuprizone caused a distal peripheral axonopathy with degeneration of myelinated axons in the sciatic nerve but preservation of the spinal nerve roots, dorsal root ganglia, posterior spinal funiculi and anterior horn cells. Cycloleucine caused intramyelinic vacuolation only in the CNS myelin and a severe distal axonal, predominantly motor, neuropathy.

The cause for the distal axonal, predominantly motor, degeneration is still enigmatic. Distal axonopathy ('dying back') was thought to result from impaired metabolism of the perikaryon of the nerve cell, but focal abnormalities in distal axonal metabolism might also produce this change. Cavanagh (1979) classified distal axonal neuropathy into groups: (1) energy-dependent; (2) pyridoxine dependent; (3) (*a*) filamentous, (*b*) vacuolo-membranous. The axonal neuropathy caused by CL has some similarity to Group 3 (*b*). Organophosphates, which cause an inhibition of cholinesterase, lead to selective damage to large diameter, long fibres in the CNS and PNS. In the early stages, before wallerian-type degeneration, membranous accumulations were found in axons, an abnormality not found in CL-induced axonopathy.

S-adenosylmethionine is known to be the sole methyl donor in many transmethylation reactions in the nervous system, involving neurotransmitters, amines and polyamines, membrane phospholipid, protein and nucleoprotein (Baldessarini, 1987). Since SAM is essential for the methylation of membrane lipid (phophatidylcholine), decreasing microviscosity and normalizing cell membranes, failure of methylation will lead to their breakdown, especially in the presynaptic axolemma of motor end-plates where there is a high membrane turnover during transmitter release (Heuser and Reese, 1973). The failure of methylation of RNA, neurotransmitters and choline may also play a role in distal axonal degeneration.

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ANNOUNCEMENTS

Courses

The following courses are being organized by the Institute of Psychiatry (University of London), the Maudsley Hospital and Bethlem Royal Hospital

'Treatment and Care in Old Age Psychiatry', July 8–10, 1992.

'Sixth Annual two-day course on eating disorders', September 21–22, 1992

Women and Mental Health—Women and Community Care—a Multidisciplinary Approach', November 26–27, 1992.

For further information contact Mrs Lee Wilding, Conference Office, Institute of Psychiatry, De Crespigny Park, London SE5 8AF (Tel 071 703 5411, ext. 3170; Fax: 071 703 5896).

The Medical College of Wisconsin and Continuing Medical Education, Inc. announce the seventh in a series of courses 'The Sharper Image in MRI' MR Angiography and Imaging of the Head, Spine and Musculoskeletal System, July 27–31, 1992, at the Broadmoor Resort in Colorado Springs, Colorado, USA. Fees: $495.00 before June 5, 1992, $545 00 after June 5, 1992 Contact: Marti Carter, CME, Inc., 11011 W. North Avenue, Milwaukee, WI 53226, USA (Tel 414 771-9520).

Conferences organized by The New York Academy of Sciences

'The Neurohypophysis: a Window on Brain Function' at Dartmouth College, Hanover, New Hampshire, USA, July 16–20, 1992.

'The Melanotropic Peptides' at Palais des Congrès, Place de la Cathédrale, Rouen, France, September 6–9, 1992

'Symposium on Temporal Information Processing in the Nervous System with Special Reference to Dyslexia and Dysphasia' at Vista Hotel, New York City, USA, September 13–16, 1992

'The Role of Insulin-like Growth Factors in the Nervous System' at Crystal Gateway Marriott, Arlington, Virginia, USA, November 4–7, 1992

'Molecular Basis of Ion Channels and Receptors involved in Nerve Excitation, Synaptic Transmission and Muscle Contraction' at the Ibuka Memorial Hall, Waseda University, Tokyo, Japan, January 12–15, 1993.

For further information contact the Conference Department, The New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021, USA (Tel· 212 838-0230; Fax: 212 888-2894).

The Eleventh Annual Scientific Meeting and Exhibition of the Society of Magnetic Resonance in Medicine

This meeting will be held in Berlin, Germany, August 8–14, 1992 For further information contact SMRM, 1918 University Avenue, Suite 3C, Berkeley, CA 94704, USA (Tel: 510 841-1899; Fax. 510 841-2340).

Ultrasound Angiography 92—2nd International Conference

This conference will be held in the Medical and Biological Sciences Building, University of Southampton, UK, September 2–4, 1992 For further information contact Conference Secretariat, Ultrasound Angiography 92, PO Box 15, Eastleigh, Hampshire SO5 5XG, UK.

First International Symposium on Brain Death

This symposium will be held in Havana, Cuba, September 22–25, 1992. For further information contact 1st International Symposium on Brain Death, Palacio de las Convenciones, Apartado 16046, La Habana, Cuba (Telex: 511609 palco cu, Fax: 22-2382.

The Second International Congress on Objective Assessment in Rehabilitation Medicine—Low Back Pain and Brain Injury

This congress will be held in Montréal, Québec, Canada, October 5–6, 1992. For further information contact Centre de formation en réadaptation du Québec, 6300 Avenue Darlington, Montréal, Québec, Canada H3S 2J4 (Tel: 514 340-2089; Fax: 514 340-2149)

International Congress on Neurology and Neurosurgery at the Third International Symposium on Epilepsy

These two events will be held in Havana, Cuba, December 7–11, 1992. For further information contact Professor Otto Hernández Cossio, President of the Organizing Committee, Apartado 4248, Zona Postal 4, Ciudad de la Habana 10400 Cuba (Tel: 32-7825; Telex: 511609 palco cu; Fax: 22-8382 and 20-2350).

AAEM 1992 Annual Meeting

The Thirty-Ninth Annual Scientific Meeting and the Fifteenth Annual CME Courses of the American Association of Electrodiagnostic Medicine (AAEM) will be held in Charleston, South Carolina, USA, October 14–18, 1992. For information contact The AAEM Office, 21 Second Street SW, Suite 306, Rochester, MN 55902, USA (Tel: 507 288-0100; Fax: 507 288-1225).

The Eighth Conference of the South East European Society for Neurology and Psychiatry

This conference will take place in Jerusalem, Israel, February 28–March 3, 1993. For information contact Professor S. Feldman, The VIII Conference of the South East European Society for Neurology and Psychiatry, c/o PO Box 50006, Tel Aviv 61500, Israel (Tel: 972 3 5174571; Fax: 972 3 655674).

Second International Conference on Stroke

This conference will take place in Geneva, Switzerland, May 12–15, 1993. For information contact N M. Bornstein, MD, International Conference on Stroke, c/o Kuowi Travel Ltd, 7 Rue de Berne, CH-1211, Geneva 1, Switzerland (Tel. 41 22 732 0888; Fax 41 22 731 5078).

The Ninth International Symposium of Brain Edema

This symposium will be held in Tokyo (Pacifico Yokohama), Japan, May 16–19, 1993 For information contact Umeo Ito, MD, Department of Neurosurgery, Musashino Red-Cross Hospital, 1-26-1, Kyonan-cho, Musashino-shi, Tokyo 18, Japan (Tel: 81-422-32 3111; Fax: 81-422-32 3525)

Seventh World Congress on Pain

This congress, sponsored by the International Association for the Study of Pain, will be held in Paris, France, August 22–27, 1993. For information contact Louisa E. Jones, International Association for the Study of Pain, 900, NE 43rd Street, Suite 306, Seattle, WA 98105, USA (Tel: 206-547-6409, Fax: 206-547-1703)

Thirteenth International Congress of EEG and Clinical Neurophysiology

This congress, organized by The International Federation of Clinical Neurophysiology, will be held in Vancouver, BC, Canada, August 29–September 4, 1993 For further information contact Information Secretariat, 645-375 Water Street, Vancouver, BC, Canada, V6B 5C6 (Tel: 604-681-5226, Fax. 604-681-2503).

The Sixth Congress of the European College of Neuropsychopharmacology

This congress will take place in Budapest, Hungary, October 10–14, 1993. For information contact Peter Gaszner, Hüvosvolgyi út 116, Budapest, H-1021, Hungary *or* Congress Bureau MOTESZ, Ms Krisztina Szigedi (Tel: 361 251-7999, 163-0037, 163-3899; Fax. 361 183-7918).

Foundation Fyssen 1992 International Prize

The deadline for nominations for this prize is September 1, 1992. Subject considered: biological mechanisms of cognitive development For information contact Colette Leconte, Executive Secretary, Foundation Fyssen, 194 rue de Rivoli, 75001 Paris, France (Tel: 33 (1) 42 97 53 16, Fax· 33 (1) 42 60 17 95).

Volvo Award for CNS Injury Research, 1993 by the Neurotraumatology Committee of the World Federation of Neurosurgical Societies

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British Journal of Developmental Psychology
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This new journal, launched in 1983, publishes authoritative scientific articles describing all aspects of development from infancy to old age, including educational implications and the problems of abnormal development.
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British Journal of Mathematical and Statistical Psychology
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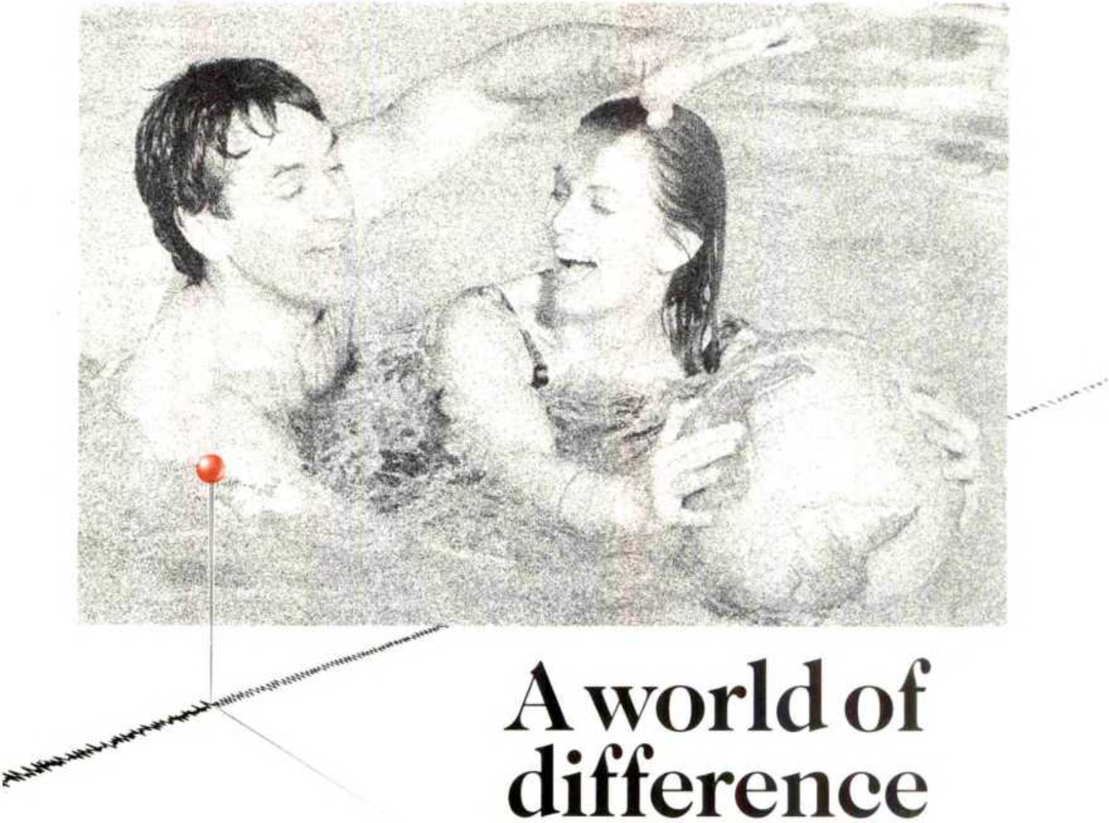

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QUINOLINIC ACID AND KYNURENINE PATHWAY METABOLISM IN INFLAMMATORY AND NON-INFLAMMATORY NEUROLOGICAL DISEASE

by M. P. HEYES,[1] K. SAITO,[1] J. S. CROWLEY,[1] L. E. DAVIS,[9] M. A. DEMITRACK,[2] M. DER,[6] L. A. DILLING,[15] J. ELIA,[3] M. J. P. KRUESI,[3] A. LACKNER,[10] S. A. LARSEN,[11] K. LEE,[1] H. L. LEONARD,[3] S. P. MARKEY,[1] A. MARTIN,[4] S. MILSTEIN,[5] M. M. MOURADIAN,[7] M. R. PRANZATELLI,[12] B. J. QUEARRY,[1] A. SALAZAR,[13] M. SMITH,[10] S. E. STRAUSS,[8] T. SUNDERLAND,[4] S. W. SWEDO[3] *and* W. W. TOURTELLOTTE[14]

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SUMMARY

Neurological dysfunction, seizures and brain atrophy occur in a broad spectrum of acute and chronic neurological diseases. In certain instances, over-stimulation of *N*-methyl-D-aspartate receptors has been implicated. Quinolinic acid (QUIN) is an endogenous *N*-methyl-D-aspartate receptor agonist synthesized from L-tryptophan via the kynurenine pathway and thereby has the potential of mediating *N*-methyl-D-aspartate neuronal damage and dysfunction. Conversely, the related metabolite, kynurenic acid, is an antagonist of *N*-methyl-D-aspartate receptors and could modulate the neurotoxic effects of QUIN as well as disrupt excitatory amino acid neurotransmission. In the present study, markedly increased concentrations of QUIN were found in both lumbar cerebrospinal fluid (CSF) and post-mortem brain tissue of patients with inflammatory diseases (bacterial, viral, fungal and parasitic infections, meningitis, autoimmune diseases and septicaemia) independent of breakdown of the blood-brain barrier. The concentrations of kynurenic acid were also increased, but generally to a lesser degree than the increases in QUIN. In contrast, no increases in CSF QUIN were found in chronic neurodegenerative disorders, depression or myoclonic seizure disorders, while CSF kynurenic acid concentrations were significantly lower in Huntington's disease and Alzheimer's disease. In inflammatory disease patients, proportional increases in CSF L-kynurenine and reduced L-tryptophan accompanied the increases in CSF QUIN and kynurenic acid. These responses are consistent with induction of indoleamine-2,3-dioxygenase, the first enzyme of the kynurenine pathway which converts L-tryptophan to kynurenic acid and QUIN. Indeed, increases in both indoleamine-2,3-dioxygenase activity and QUIN concentrations were observed in the cerebral cortex of macaques infected with retrovirus, particularly those with local inflammatory lesions. Correlations between CSF QUIN, kynurenic acid and

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L-kynurenine with markers of immune stimulation (neopterin, white blood cell counts and IgG levels) indicate a relationship between accelerated kynurenine pathway metabolism and the degree of intracerebral immune stimulation.

We conclude that inflammatory diseases are associated with accumulation of QUIN, kynurenic acid and L-kynurenine within the central nervous system, but that the available data do not support a role for QUIN in the aetiology of Huntington's disease or Alzheimer's disease. In conjunction with our previous reports that CSF QUIN concentrations are correlated to objective measures of neuropsychological deficits in HIV-1-infected patients, we hypothesize that QUIN and kynurenic acid are mediators of neuronal dysfunction and nerve cell death in inflammatory diseases. Therefore, strategies to attenuate the neurological effects of kynurenine pathway metabolites or attenuate the rate of their synthesis offer new approaches to therapy.

INTRODUCTION

Neurological symptoms and neurodegeneration are salient features of many neuropathological conditions including acute metabolic and physiological insults, chronic motor and dementia disorders, as well as inflammatory diseases, and are an important cause of morbidity and mortality in man. Although the mechanisms responsible for nerve cell death and neurological dysfunction are likely to be complex, the involvement of *N*-methyl-D-aspartate and other excitatory amino acid receptors have been implicated (Schwarcz *et al.*, 1984; Rothman and Olney, 1987; Auer and Siesjo, 1988; Young *et al.*, 1988; Meldrum and Garthwaite, 1990; Heyes *et al.*, 1991*a*). These receptors not only mediate excitatory amino acid neurotransmission within the hippocampus, basal ganglia and cerebral cortex (Cotman *et al.*, 1988), but when activated for a sufficient period of time, may also result in neurodegeneration and seizures (Rothman and Olney, 1987; Whetsell and Schwarcz, 1989; Meldrum and Garthwaite, 1990). While both glutamate and aspartate are endogenous ligands of *N*-methyl-D-aspartate receptors, the observation that quinolinic acid (QUIN) is also an excitotoxic *N*-methyl-D-aspartate receptor agonist raises the potential involvement of this metabolite in many neurodegenerative and convulsant disorders (Lapin, 1982; Perkins and Stone, 1983; Schwarcz *et al.*, 1983; Moroni *et al.*, 1986*a*; Heyes *et al.*, 1991*a*). Particular interest has focused on the role of QUIN in Huntington's disease and Alzheimer's disease because of the similarities between QUIN-induced lesions and post-mortem features of these disorders (Schwarcz *et al.*, 1983, 1984, 1988*b*; Beal *et al.*, 1986; Reynolds *et al.*, 1988; Mouradian *et al.*, 1989; Whetsell and Schwarcz, 1989; Boegman *et al.*, 1990; Heyes *et al.*, 1990*c*). It is of interest that the related metabolite, kynurenic acid (KYNA; Fig. 1) is an antagonist of *N*-methyl-D-aspartate and other excitatory amino acid receptors (Foster *et al.*, 1984). Therefore, increases in KYNA concentrations within the central nervous system (CNS) could mitigate the neurotoxic effects of QUIN and other excitotoxins while reductions in KYNA levels could promote excitotoxicity (Foster *et al.*, 1984; Beal *et al.*, 1990; Boegman *et al.*, 1990). Clearly, situations where persistent disturbances in the concentrations of QUIN and KYNA within the CNS occur are situations where their neurological and neuropathological effects may become manifested.

Quinolinic acid and KYNA are synthesized from L-tryptophan via the kynurenine pathway (*see* Fig. 1). L-Tryptophan is converted to L-kynurenine (L-KYN) by the action of tryptophan-2,3-dioxygenase (tryptophan pyrrolase) in the liver, and indoleamine-2,3-dioxygenase (IDO) in extrahepatic tissues, including brain, lung and macrophages (Gal and Sherman, 1980; Takikawa *et al.*, 1986; Saito *et al.*, 1991*b*; Taylor and Feng, 1991). Studies initiated by Hayayishi *et al.* have demonstrated that the activity of IDO is increased

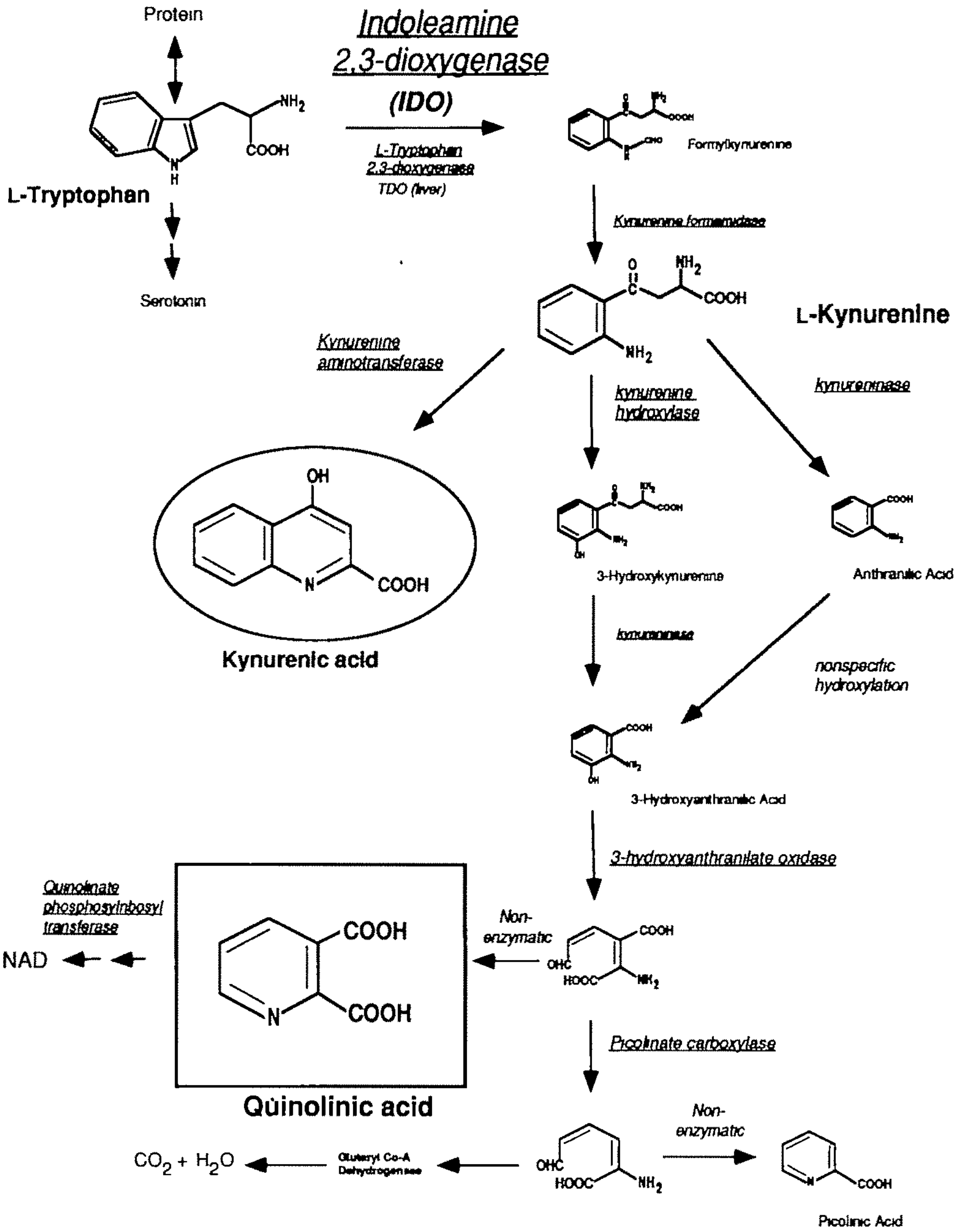

FIG. 1. General overview of tryptophan and kynurenine metabolic pathways. Note: indoleamine-2,3-dioxygenase (IDO) occurs in extrahepatic tissues, including brain, whereas tryptophan-2,3-dioxygenase (tryptophan pyrolase) is localized in the liver. Although the kynurenine pathway is the major route of L-tryptophan metabolism in systemic tissues, coversion of L-tryptophan to indoles is the predominant route within the CNS. Activity of IDO is increased following immune stimulation, whereas hepatic tryptophan-2,3-dioxygenase activity is either unchanged or reduced. *See also* Fig. 9.

in many extrahepatic tissues following immune activation or interferon-γ administration (Yoshida *et al.*, 1981; Takikawa *et al.*, 1986; Saito *et al.*, 1991*b*; Taylor and Feng, 1991). Activation of IDO and accumulation of QUIN also occurs within the CNS of experimental animals following immune stimulation (Takikawa *et al.*, 1986; Heyes *et al.*, 1988*b*, 1989), and these responses are sustained by repeated administration of interferon-γ (Saito *et al.*, 1991b). This cytokine is produced following immune activation. Therefore, activation of IDO and production of neuroactive kynurenine pathway metabolites within the CNS may occur and persist in patients with inflammatory disease, and correlate with markers of immune activation and interferon-γ activity. To date, no study has investigated this hypothesis in humans, and interest in QUIN as a neurotoxin remains focused on non-inflammatory neurological disease.

In the present study, CSF QUIN and KYNA concentrations were quantified in patients with either inflammatory or non-inflammatory neurological diseases. To determine whether QUIN concentrations are increased in brain areas which contain *N*-methyl-D-aspartate receptors, regional brain QUIN levels were also measured. Because the duration of exposure influences the neurotoxicity of QUIN (Whetsell and Schwarcz, 1989), serial samples of CSF were studied from patients who were infected with the human immunodeficiency virus type-1 (HIV-1). In certain instances, additional clinical and biochemical data were available to investigate mechanisms that could affect CSF QUIN and KYNA levels. Activity of IDO was quantified directly in samples of cerebral cortex from macaques infected with retrovirus and evaluated indirectly in humans by measuring CSF L-KYN levels. Immunoglobulin (IgG) and white blood cell counts were measured in the CSF as 'markers' of intracerebral immune stimulation. Neopterin was measured in the CSF as a surrogate marker of interferon-γ activity (Fuchs *et al.*, 1989). The integrity of the blood-brain barrier was investigated by measuring protein, albumin and IgG concentrations in the CSF and blood (Tibbling *et al.*, 1977).

MATERIALS AND METHODS

Samples of CSF were obtained from eight clinical centres in the United States and Canada, each specializing in studies of specific types of neurological disease. Samples were collected after a standard meal and overnight bedrest between 08.00 and 10.00 unless othewise stated. Patients were classified into five separate groups based on both age and the presence or absence of known immune stimuli. Informed consent was given by patients or close relatives to obtain some of these samples; others were obtained during routine neurological investigations.

Cerebrospinal fluid

Non-inflammatory neurological disease

Group I. Group I patients were neurologically normal adult volunteers (aged 59.1 ± 14.2 yrs; n = 30) and medication-free patients with either Huntington's disease (aged 49.4 ± 4.5 yrs; n = 13), Alzheimer's disease (aged 63.8 ± 1.2 yrs; n = 39), olivopontocerebellar atrophy (aged 52.9 ± 5.9 yrs; n = 10), progressive supranuclear palsy (aged 62.9 ± 1.2 yrs; n = 11) or depression (53.5 ± 3.8 yrs; unipolar n = 7, or bipolar n = 3). The durations of clinical illness were: 10 ± 7.3 yrs, 4.3 ± 2.5 yrs, 11.7 ± 5.7 yrs, 3.3 ± 1 yrs and 17.6 ± 3.8 yrs, respectively. The 9th millilitre aliquot or pooled 5th – 10th millilitre aliquot (depressed patients) of CSF were used for analysis. Cerebrospinal fluid concentrations gradients (between 5 ml and 22 ml) were investigated in five additional patients with Alzheimer's disease who were medication free for at least 21 d and studied in the NIMH Alzheimer Unit at 08.30 after overnight bedrest.

Group II. Younger neurologically normal adults (aged 35.2 ± 8.4 yrs; n = 16) were compared with age-matched patients with chronic fatigue syndrome (Holmes *et al.*, 1988) (37.5 ± 8.5 yrs; n = 18; duration

7.2 ± 1 yrs) or progressive myoclonus epilepsy (21.8 ± 2.2 yrs; n = 5; duration 10 ± 4.3 yrs). The pooled first 15 ml of controls and chronic fatigue syndrome patients or the pooled 3rd-5th pooled fraction of the patients with progressive myoclonus epilepsy were used.

Group III Cerebrospinal fluid (pooled 3rd – 8th millilitre) from paediatric patients with either obsessive compulsive disorder (14.1 ± 2.8 yrs; n = 24) or disruptive behaviour (10.7 ± 3.4 yrs; n = 30), who were without seizure disorder or fever, were compared wth infants and children with several juvenile non-inflammatory neurological diseases studied on an outpatient basis (6.1 ± 4.4 yrs, pooled 3rd – 5th millilitre): essential myoclonus (n = 1), myoclonus encephalopathy (n = 1), opsoclonus myoclonus (n = 1), seizure disorder (n = 6), headache (n = 4; 9.2 ± 2.5 yrs), developmental delay (n = 3; 4.7 ± 2 yrs), chronic chorea/athetosis (n = 2, 5, 9 yrs), Alexander's leukodystrophy (n = 1; 0.5 yrs), Batten's disease (n = 1, 14 yrs) or Pompe's glycogenosis (n = 1; 0.6 yrs). Seizures were diagnosed by clinical criteria and electroencephalogram (EEG) with other tests described for progressive myoclonus epilepsy cases. Six patients with glutaric aciduria type-1 (Goodman *et al.*, 1977) were also studied. Their glutaryl Co-A dehydrogenase activity was either 1% (n = 4, age 6.1 ± 1.8 yrs) or 10% (n = 2, age 10 yrs and 0.9 yrs) of normal, and all six had a positive family history and typical neurological signs. This enzyme deficiency was predicted to increase QUIN concentrations (Heyes, 1987).

Inflammatory neurological disease

Group IV Cerebrospinal fluid was obtained during evaluation of overt dementia, seizures, motor disturbances or suspected meningeal involvement from 36 patients with a broad spectrum of inflammatory conditions (Table 1). Various CSF fractions were used and samples were collected at different times throughout the day.

Group V. Cerebrospinal fluid was collected on an outpatient basis from patients in the early stages of HIV-1-infection, as part of a longitudinal study of the neurobehavioural consequences of HIV-infection. Patients were classified by the Walter Reed (WR) staging system of HIV-1 disease (Redfield *et al.*, 1986) which is based on quantitative measures of immunological status and symptoms (31.1 ± 6.7 yrs; n = 56): WR 1, n = 8 samples; WR 2, n = 51; WR 3, n = 22; WR 4, n = 7; WR 5, n = 15). None of the patients demonstrated overt dementia or other clinical neurological impairments, although approximately 33% of patients had subtle cognitive and motor impairments (Martin *et al.*, 1990).

Brain tissue

Samples of brain (as coronal brain slices) were obtained from the National Neurological Research Bank, Los Angeles, CA and stored at −70°C until analysed. Patients were classified as having inflammatory disease or sepsis (aged 50.5 ± 4.6 yrs; autolysis time, 16.8 ± 2.8 h) or non-inflammatory disease (aged 58.8 ± 5 yrs; autolysis time, 18.5 ± 1.6 h). Their diagnoses were based on clinical history and neurohistopathological examination; cause of death was variable. Non-inflammatory disease: suicide (hanging); schizophrenia (n = 2; barbiturate suicide or pulmonary emboli); Huntington's disease (n = 2; both pneumonia); Alzheimer's disease (n = 1; aspiration pneumonia); Parkinson's disease (n = 2; both bronchopneumonia); amyotropic lateral sclerosis (n = 3; all respiratory failure); inflammatory disease or sepsis: herpes encephalitis (n = 1; temporal lobe encephalomalacia and chronic lymphocytic leukaemia); HIV-1 infection (n = 2; both septicaemia and either *Pneumocystis carinii* pneumonia or Hodgkin's disease); multiple sclerosis (n = 1; pneumonia), viral encephalitis (n = 1; bronchopneumonia with perivascular cuffing and astrogliosis in brainstem), septicaemia with advanced Alzheimer's disease and Parkinson's disease (n = 1). Brain slices were placed in a freezer at −20°C for 18 h and samples of cerebral cortex, cerebellum, hippocampus, caudate nucleus, putamen, globus pallidus and white matter were collected.

Brain IDO activity and QUIN concentrations were also determined in retrovirus-infected macaques (*Macacca mulatta*). The macaques studied were: (i) controls, healthy uninfected macaques (n = 6) and macaques with either chronic colitis or failure to thrive (n = 9); (ii) antibody positive/virus negative for type-D retrovirus (recovered, n = 6); (iii) virus positive for type-D retrovirus (n = 9); (iv) virus positive for simiain immunodeficiency virus (SIV, either SIV$_{sm}$, SIV$_{mac\text{-}239}$, SIV$_{mac\text{-}1A11}$ or SIV$_{sm}$+type-D retrovirus) administered either via intravenous, intramuscular or vaginal routes (Heyes *et al.*, 1990*b* Sutjipto *et al.*, 1990; Lackner *et al.*, 1991; n = 25). Simian immunodeficiency virus-infected macaques were classified as having: (*a*) no inflammatory CNS lesions (n = 12); (*b*) subcortical or meningeal inflammatory lesions (n = 3); (*c*) inflammatory lesions in the cerebral cortex adjacent to samples used for biochemical analyses (n = 10). The time between euthanasia, sample freezing and storage prior to the biochemical assays was

TABLE 1 CLINICAL DIAGNOSES, CHARACTERISTICS AND CSF QUIN CONCENTRATIONS OF PATIENTS WITH INFLAMMATORY DISEASES

Patient no	*Age*	*Gender*	*Neurological diagnosis*	*Additional clinical history*	*CSF QUIN (nM)*
Meningeal inflammation					
1	18	F	Aseptic meningitis	Unidentified viral encephalitis?	75
2	68	M	Coccidioidomycosis	Chronic pulmonary fibrosis	85
3	21	F	*Staphylococcus aureus* VP shunt infection, hydrocephalus		110
4	14	M	*Haemophilus influenzae* bacterial meningitis		300
5	26	M	Acute lymphoblastic leukaemic meningitis		304
6	0 2	M	Viral meningitis		386
7	6	M	*H. influenzae* bacterial meningitis		591
8	0 1	M	Enterovirus meningitis		889
9	0 2	M	Viral meningitis		1838
10	63	M	Listerial meningitis	Chronic lymphocytic leukaemia	2508
11	30	F	Neurocysticercosis		2887
12	28	M	Viral meningitis		3768
T 13	30	M	Aseptic meningitis		4955
Parenchyma inflammation					
14	52	F	Cerebral lupus	Transient chorea, hypertension, obesity	54
15	33	M	CNS viral syndrome and sarcoidosis	Fibrotic lung infiltrates	105
16	18	F	Nocardial brain abcess	Renal transplant	126
17	30	M	Temporal lobe brain abcess mixed streptococci		151
18	35	M	Multiple sclerosis acute attack		186
19	44	M	Post viral encephalitis; oral candidiasis	Amnesia following flu-like syndrome	279
20	61	M	Viral encephalitis	Paraneoplastic bronchopneumonia	322
21	56	F	CNS vasculitis	Systemic lupus erythmatosus, oral candidiasis	2044
Septicaemia					
22	76	M	Sepsis	Basal cell carcinoma	140
23	74	F	Sepsis with diffuse cerebral dysfunction		180
24	59	M	*Candida albicans* sepsis	Coronary artery disease, renal failure	1184
25	82	M	Sepsis	Pneumonia, congenital heart failure, liver cirrhosis	1419
26	85	M	Sepsis (perforated ileum)	Chronic obstructive lung disease, glaucoma, aspiration pneumonia	1522
27	64	M	*S aureus* septicaemia	Chronic obstructive lung disease	2350
Other inflammatory diseases					
28	66	M	Vascular headaches, possible sarcoid meningitis	Silicosis	42
29	81	M	Guillain-Barré syndrome		57
30	48	M	Neurovascular syphylis, demyelination, hemiparesis	Basal cell carcinoma	58
31	73	F	Latent syphilis and acoustic neuroma	Acoustic neuroma, dementia	361
32	32	M	Acute head injury	Glomerular nephritis	710
33	34	M	Closed head trauma		1938
34	80	M	Sepsis (perforated ileum), herpes encephalopathy, anoxic encephalopathy, fibrous leptomeninges	Lymphocytic leukaemia	2157
35	39	M	Human immunodeficiency virus infection and opportunistic *Cryptococcus neoformans* meningitis		4996
36	73	M	Cryptococcal meningitis and sepsis	Liver cirrhosis, chronic obstructive lung disease	17 512

Patients were classified as having either meningeal inflammation, brain parenchyma inflammation, septicaemia or other CNS inflammatory disease Normal CSF QUIN concentrations range from 8 nM to 35 nM comparable in the four groups of macaques. Histopathological examination and major histocompatibility complex class II antigen (class II) expression was also evaluated (Lackner *et al.*, 1991). Inflammatory lesions of the cerebral cortex are defined by the presence of perivascular monocyte infiltrates, microglial nodules or multinucleated giant cell infiltrates and increased staining for class II. Cerebrospinal fluid and serum samples were also collected throughout the course of disease in 12 SIV-infected macaques.

Biochemical and statistical analyses

All samples were analysed with established methods by experienced laboratory personnel without knowledge of the clinical diagnoses (Heyes and Quearry, 1988, 1990; Heyes *et al.*, 1989, 1991*b*, 1992*a*; Saito *et al.*, 1991*b*). Total protein, albumin, IgG, T_4, T_8, white blood cell counts, red blood cell counts, glucose and the presence of bacteria, viruses and fungi were quantified by routine laboratory methods at the institutes where samples were collected.

Group mean values were compared by one-way analysis of variance with Dunnett's *t* test for multiple comparisons, and regression analysis was done by the method of least squares (Gagnon *et al.*, 1989). In the case of samples from patients and macaques with inflammatory disease, all values were analysed after transformation to their logarithm. Values presented are mean ± 1 standard error of the mean (SEM) unless otherwise stated. A value of $P < 0.05$ was considered significant. NS indicates not statistically significant. 'n' refers to the number of patients or samples studied. Some results have been presented previously (Mouradian *et al.*, 1989; Saito *et al.*, 1991*a*).

RESULTS

Cerebrospinal fluid

Confounding variables

Data were first analysed with respect to potentially confounding variables. There were no concentration gradients for CSF L-tryptophan, L-KYN, KYNA or QUIN in patients with Alzheimer's disease or in seven children with psychiatric disorders (obsessive compulsive disorder or disruptive behaviour; data not shown). Gender had no contributory effect in any control or patient group studied, as determined by analysis of variance. It is unlikely that non-specific stress contributed to disturbances in CSF QUIN levels, as concentrations in patients with the following diseases that could be viewed as 'stressful', had levels of CSF QUIN comparable to neurologically normal age-matched control volunteers (10–35 nM; *see below*): depressive illness, 25 ± 3.6 nM; myoclonus epilepsy, 18.1 ± 2.2 nM; the inter-ictal and post-ictal periods of complex partial seizures (Heyes *et al.*, 1990*c*), anorexia nervosa (Demitrack *et al.*, 1990) and bulimia nervosa (Demitrack *et al.*, 1990). Furthermore, patients with chronic neurodegenerative diseases are also 'controls' for stress, as well as for brain atrophy, gliosis, dementia and motor disturbances (*data presented below*), while patients with myoclonus epilepsy, or complex partial seizures (Heyes *et al.*, 1990*c*) are 'controls' for seizures. Almost all samples were collected in the morning. It is also unlikely that disturbances in food intake can account for the differences in patients with inflammatory diseases as patients with either anorexia nervosa or bulimia nervosa do not have elevated CSF L-KYN, KYNA or QUIN concentrations (Demitrack *et al.*, 1990).

Age

Lumbar CSF QUIN concentrations were correlated with age (Fig. 2) in Group I controls, Group II controls and in patients with chronic fatigue syndrome (r = 0.48, $P < 0.05$, data not shown). Group I controls were older than Group II controls (59.1 ± 14.2 yrs versus 32.5 ± 8.4 yrs) and CSF QUIN concentrations were significantly

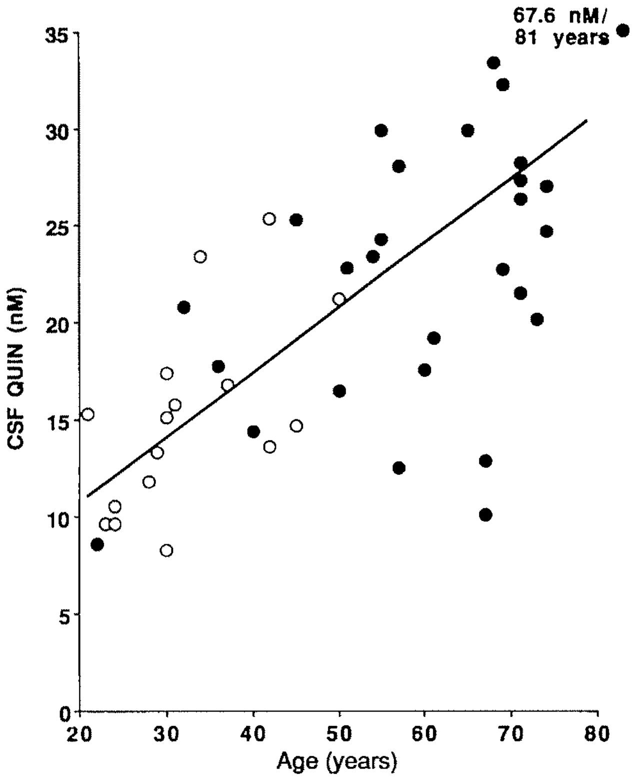

FIG. 2. Positive correlation between age and lumbar CSF QUIN concentrations in two groups of neurologically normal control subjects. Group I. r = 0.49, $P < 0.01$ (closed circles), Group II r = 0.59, $P < 0.01$ (open circles). Regression line is for the combined data (r = 0.65, $P < 0.0001$).

higher in Group I (Group I, 23.5 ± 2 nM versus Group II, 15.1 ± 1.2 nM; $P < 0.001$). However, in patients below 21 yrs of age, there were no correlations between CSF QUIN and age in three cohorts studied. Age was not correlated with CSF measures of L-tryptophan, L-KYN and KYNA in any control or patient group.

Non-inflammatory neurological disease

Group I. Chronic neurodegenerative diseases. There were no significant differences in lumbar CSF QUIN concentrations in patients with either Huntington's disease, Alzheimer's disease, olivopontocerebellar atrophy or progressive supranuclear palsy when compared with age-matched Group I controls (Fig. 3). There were no correlations between CSF L-tryptophan, L-KYN, KYNA or QUIN concentrations with duration of clinical disease. Cerebrospinal fluid L-KYN and KYNA levels were lower in Huntington's disease, while KYNA was lower in Alzheimer's disease. Cerebrospinal fluid QUIN concentrations correlated with both L-KYN (r = 0.81, $P < 0.005$) and KYNA (r = 0.61, $P < 0.05$) in Huntington's disease, while CSF L-KYN levels correlated with CSF KYNA in Alzheimer's disease (r = 0.46, $P < 0.01$). There were no metabolite correlations in the neurologically normal control subjects.

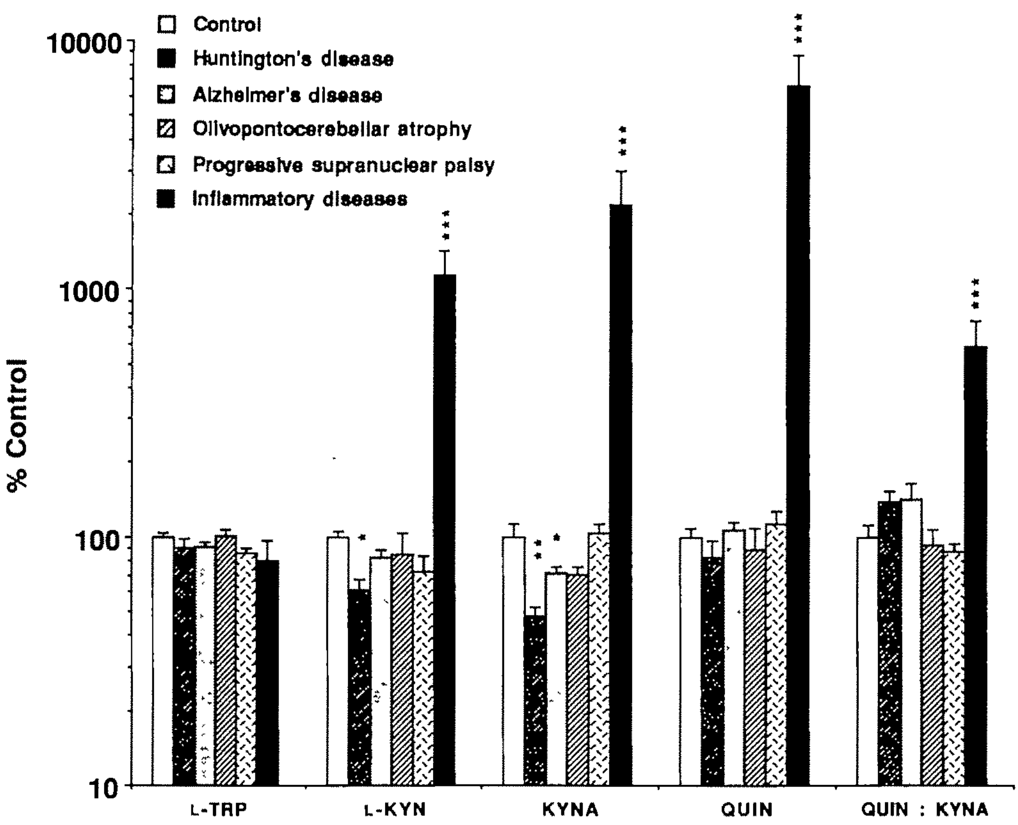

FIG. 3. Comparison of lumbar CSF L-tryptophan (L-TRP), L-KYN, KYNA, QUIN and QUIN : KYNA ratio in patients with either Huntington's disease (n = 30), Alzheimer's disease (n = 39), olivopontocerebellar atrophy (n = 10), progressive supranuclear palsy (n = 11), and patients with a broad spectrum of inflammatory diseases (n = 36, *see* Table 1) plotted as a percentage of Group I control subjects (n = 30). Data and ±1 SEM are plotted after transformation to the logarithm. The bar code is presented in the key. Control values ±1 SEM of the Group I subjects were. L-TRP, 2.32±0.09 μM; L-KYN, 52.9±3 1 nM: KYNA, 3.49±0.44 nM; QUIN, 23.5±2 nM and QUIN : KYNA ratio, 8.71±0.98 $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0\ 0001$ versus Group I controls.

Group II. Chronic fatigue syndrome. Patients with chronic fatigue syndrome had slightly higher lumbar CSF QUIN ($P = 0.05$) and neopterin ($P < 0.05$) concentrations than age-matched neurologically normal volunteers (Fig. 4). There were no correlations between QUIN, KYNA, L-tryptophan or neopterin in control subjects. In patients with chronic fatigue syndrome, however, CSF QUIN correlated with both L-KYN ($r = 0.72$, $P < 0.001$) and neopterin ($r = 0.56$, $P < 0.02$). Cerebrospinal fluid L-KYN correlated with neopterin ($r = 0.55$, $P < 0.01$).

Group III. Pediatric patients. Children with non-inflammatory neurological disease had CSF QUIN concentrations ranging from 8.7 nM to 33.2 nM (mean 18.8±1.6 nM), which were not significantly different from children with either disruptive behaviour (16.8±0.6 nM) or obsessive compulsive disorder (17.6±1 nM). Cerebrospinal fluid QUIN levels were significantly higher in the children with glutaric aciduria (40.4±9.2 nM; $P < 0.01$).

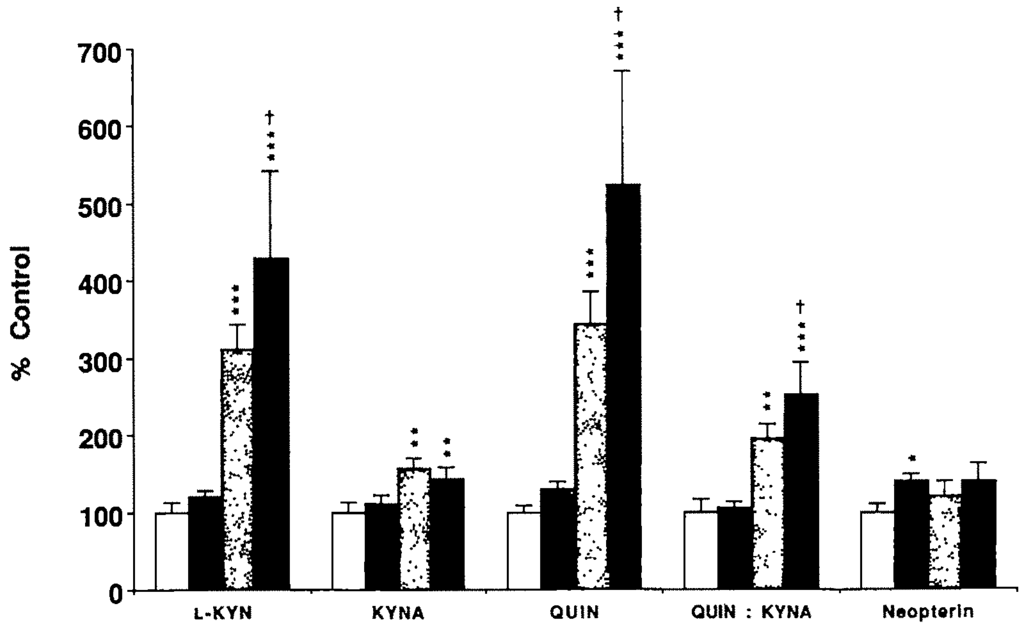

FIG. 4. Linear plot of lumbar CSF L-KYN, KYNA, QUIN and QUIN KYNA ratio in young neurologically normal Group II controls (aged 32.5 ± 2 1 yrs; n = 16; open bars), patients with chronic fatigue syndrome (aged 37 5 ± 2. yrs; n = 18, hatched bars) and HIV-infected patients classified as having either >400 T_4 cells/μl (WR 1–2, aged 29.8 ± 1.1 yrs; n = 32; stippled bars) or <400 T_4 cells/μl (WR 3–5, aged 33.8 ± 1.2 yrs, n = 23; closed bars) Among the HIV-1-infected patients, where more than one CSF sample was available within each WR stage, the mean value within each stage was used in the calculation of group mean values. If the patient changed WR stage, however, values from the different stages were used in the calculation of group mean values. Control values ± 1 SEM of the Group II subjects were L-KYN 33.2 ± 2.8 nM, KYNA 2.23 ± 0.28 nM, QUIN 15 1 ± 1.2 nM and QUIN : KYNA ratio 8.72 ± 1.46 $^{*}P < 0.05$, $^{**}P < 0.001$ and $^{***}P < 0.0001$ versus age-matched Group II controls, $^{\dagger}P < 0.001$ versus HIV-1 infected patients with >400 T_4 cells/μl by one-way analysis of variance after log transformation.

Inflammatory neurological disease

Group IV. Cerebral and meningeal inflammation and sepsis. Individual CSF QUIN concentrations for the inflammatory disease patients are listed in Table 1. There were no significant differences in CSF L-tryptophan, L-KYN, QUIN, KYNA or the ratio of QUIN : KYNA in the four classifications of inflammatory diseases, and so the data were pooled for the purposes of statistical analyses. Mean values for CSF L-tryptophan, L-KYN, QUIN, KYNA and the ratio of QUIN : KYNA are plotted on a logarithmic scale for comparison with patients with chronic neurodegenerative diseases (Fig. 3). Substantial elevations in the concentrations of QUIN, KYNA and L-KYN and increases in the QUIN : KYNA ratio were found in the CSF patients with inflammatory diseases. Cerebrospinal fluid L-tryptophan levels tended to be reduced. There were significant correlations between CSF L-KYN, QUIN, KYNA and neopterin (Table 2). In 34 of the 36 patients where white blood cell counts were available: 16 patients had < 10 cells/mm^3, seven patients had between 10 and 100 cells/mm^3, eight patients had between 100 and 1000 cells/mm^3 and two patients had > 1000 cells/mm^3. In these patients, taken collectively, significant correlations were found between white blood

TABLE 2. CEREBROSPINAL FLUID PROFILES FOR PATIENTS WITH INFLAMMATORY NEUROLOGICAL DISEASES

	KYNA	*QUIN*	*IgG*	*WBC count*	*Albumin*	*CSF: serum albumin*
L-KYN	0.72 $P < 0.0001$ (n = 24)	0.73 $P < 0.0001$ (n = 24)	NS	0.59 $P < 0.005$ (n = 21)	NS	NS
KYNA		0.80 $P < 0.0001$ (n = 30)	0.56 $P < 0.05$ (n = 14)	0.51 $P < 0.01$ (n = 27)	NS	NS
QUIN			0.54 $P < 0.05$ (n = 18)	0.40 $P < 0.05$ (n = 32)	NS	NS
IgG				0.63 $P < 0.05$ (n = 15)	NS	NS

Significant intercorrelations between CSF L-KYN, KYNA, QUIN, IgG and white blood cell (WBC) counts in patients with a wide spectrum of inflammatory disease caused by infection with either bacteria, virus, fungi or parasites as well as autoimmune diseases and physical injury to the CNS (Table 1; Fig. 3). Regression analyses were performed by the method of least squares in the data set as a whole after log transformation. NS = not significant.

cell count and CSF QUIN, KYNA, L-KYN and IgG (Table 2). Notably, there were no relationships between these measures with CSF total protein or CSF albumin concentrations.

Group V. HIV-1 infection. Cerebrospinal fluid L-KYN, KYNA and QUIN concentrations were increased in both early (>400 T_4 cells/μl of blood; WR stages 1 and 2) and later stage (<400 T_4 cells/μl of blood; WR stages 3–5) HIV-1-infected patients compared with age-matched control subjects (Fig. 5). Five of eight samples (four of five patients) in WR 1 (>400 T_4 cells/μl without any HIV-related signs or symptoms) and 51 of 59 samples (41 of 51 patients) in WR 2 (>400 T_4 cells/μl with only chronic lymphadenopathy) had CSF QUIN concentrations >2 SD above the mean of the age-matched Group II control subjects. The ratio of QUIN : KYNA was significantly higher in all WR stages (to $P < 0.05$, Fig. 4). Neopterin concentrations in CSF were slightly elevated in both groups of patients. There were significant correlations between CSF L-KYN, KYNA, QUIN, neopterin, IgG and blood $T_4 : T_8$ ratio (Table 3). Cerebrospinal fluid L-KYN and QUIN concentrations remained elevated to 2 SD above control subjects (Fig. 5A,C), whereas CSF KYNA concentrations remained within the normal range in most patients (Fig. 5B). Over time, CSF L-KYN, KYNA and QUIN tended to be elevated to the same degree within any given patient, as indicated by the significant correlations in CSF concentrations between the first sample (at time = 0) and samples at 6 mths (all $P < 0.0001$) and 12 mths (all $P < 0.001$).

Importantly, the blood-brain barrier was intact in the majority of HIV-1-infected patients as CSF albumin concentrations were within normal limits (<55) in 61 of 77 samples studied, and the ratio of CSF albumin : serum albumin was normal (< 0.017) in 39 of 41 samples studied (mean ± 2 SD: 0.010 ± 0.007) (Tibbling *et al.*, 1977). Unlike the Group IV inflammatory disease patients who had appreciable pleocytosis, white blood cell counts were within normal limits (<5 cells/mm^3) in 54 of 76 HIV-1-infected

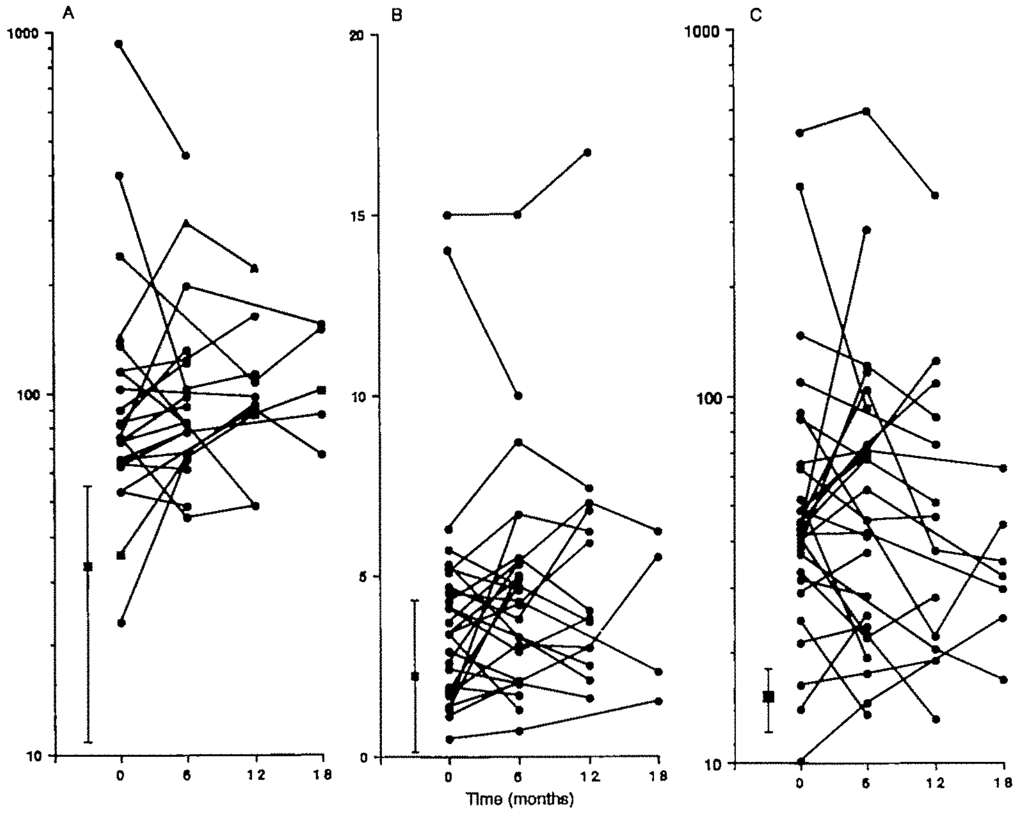

FIG 5 Lumbar CSF L-KYN (A), KYNA (B) and QUIN (C) concentrations in patients infected with HIV-1, samples collected at 6–12 mth intervals. Values presented are individual CSF QUIN concentrations and serial samples from the same patient are connected. Concentrations in control subjects (closed square) are mean ±2 SD (error bar) Note transformation of the abscissa to logarithm in (A) and (C).

TABLE 3. CEREBROSPINAL FLUID PROFILES FOR PATIENTS WITH THE HUMAN IMMUNODEFICIENCY VIRUS

	KYNA	*QUIN*	*Neopterin*	*IgG*	*Albumin*	*CSF:serum albumin*	*T4:T8 ratio*
L-KYN	r = 0.40 *P* < 0.0005 (n = 78)	r = 0.65 *P* < 0.0001 (n = 82)	r = 0.32 *P* < 0.05 (n = 40)	r = 0.47 *P* < 0.005 (n = 37)	NS	NS	r = 0.37 *P* < 0.005 (n = 61)
KYNA		r = 0.50 *P* < 0.0001 (n = 100)	r = 0.61 *P* < 0.0005 (n = 32)	NS	NS	NS	r = 0.29 *P* < 0.01 (n = 76)
QUIN			r = 0.56 *P* < 0.001 (n = 34)	r = 0.45 *P* < 0.002 (n = 49)	NS	NS	r = 0.38 *P* < 0.001 (n = 79)

List of inter-correlations between CSF L-KYN, KYNA, QUIN and neopterin in HIV-1-infected patients (Figs 4, 5). Regression analyses were performed after log transformation CSF:serum albumin ratios and WBC counts were normal in 95% and 71%, respectively, of patients studied. NS = not significant.

patients studied. Consequently, there were no correlations between CSF protein, CSF albumin, CSF : serum albumin ratio or white blood cell counts with CSF QUIN, KYNA, L-KYN or neopterin concentrations (Table 3).

Brain tissue

Human studies

Patients with inflammatory disease had substantially higher QUIN concentrations throughout the brain than patients with non-inflammatory neurological disease (Fig. 6). In the control subjects, there were no clear differences in regional brain QUIN concentration, although white matter values tended to be lower than adjacent grey matter structures. In the 11 non-inflammatory control patients, frontal cortex and cerebellum 3-hydroxykynurenine levels were < 100 pmol/g in 10 patients and was > 1000 pmol/g in one patient, but there was no correlation between 3-hydroxykynurenine and QUIN concentrations. In the six patients with inflammatory CNS disease, 3-hydroxykynurenine concentrations were < 100 pmol/g in four patients and > 1000 pmol/g in two patients.

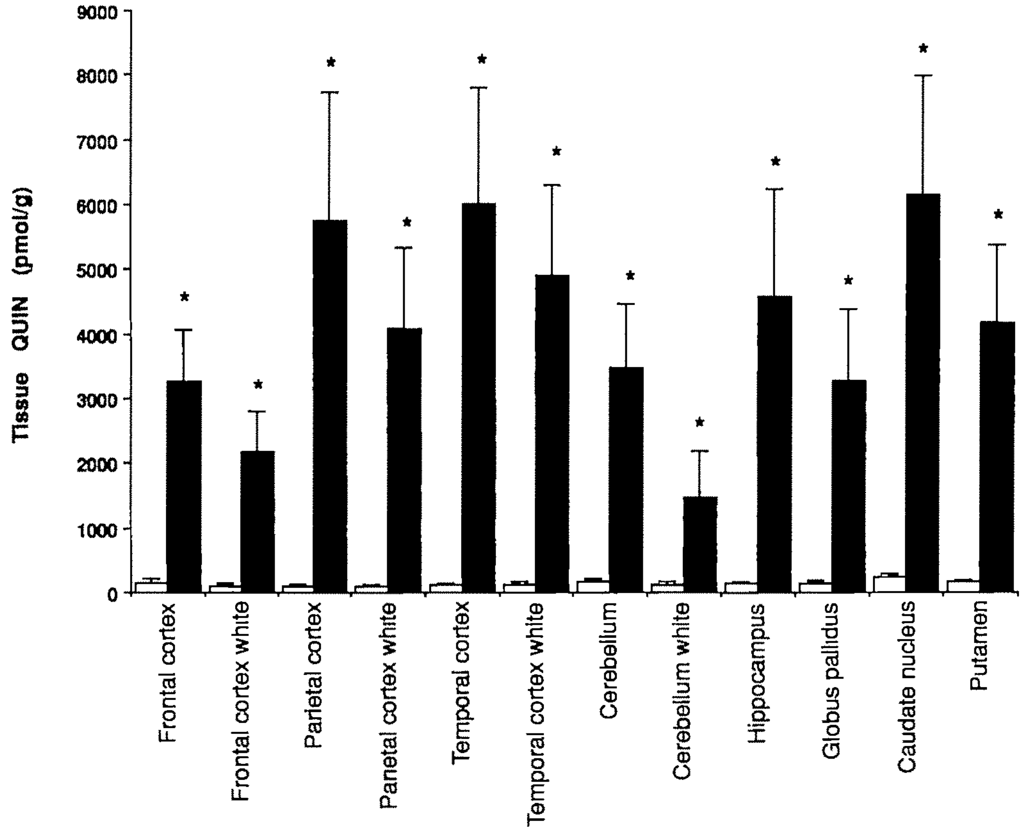

FIG. 6 Regional brain QUIN concentrations in patients with non-inflammatory (n = 11, open bars) and inflammatory neurological disease (n = 6, closed bars) Values presented are mean ± 1 SEM $*P < 0.0001$ versus controls.

Again there was no correlation between 3-hydroxykynurenine and QUIN levels and concentrations of 3-hydroxykynurenine.

Macaque studies

Activity of IDO and QUIN levels in cerebral cortex as well as cisternal QUIN concentrations were substantially increased in the SIV-infected macaques compared with either control or type-D retrovirus infected macaques (Fig. 7). The highest values were found in the macaques with SIV-related inflammatory lesions. Activity of IDO was highly correlated to cerebral cortex QUIN levels (r = 0.85, $P < 0.0001$; Fig. 8). There was also a significant correlation between QUIN levels in cerebral cortex and CSF (r = 0.55, $P < 0.005$). The time course and magnitude of the increases in QUIN, KYNA and L-kynurenine followed the same pattern as that noted previously (Heyes *et al.*, 1990*a*,*b*, 1992*a*). As in the case of patients with inflammatory disease, the concentrations of L-KYN in CSF were highly correlated with QUIN (r = 0.88, $P < 0.0001$) and KYNA (r = 0.83, $P < 0.0001$), while CSF QUIN was correlated with KYNA (r = 0.62, $P < 0.0001$).

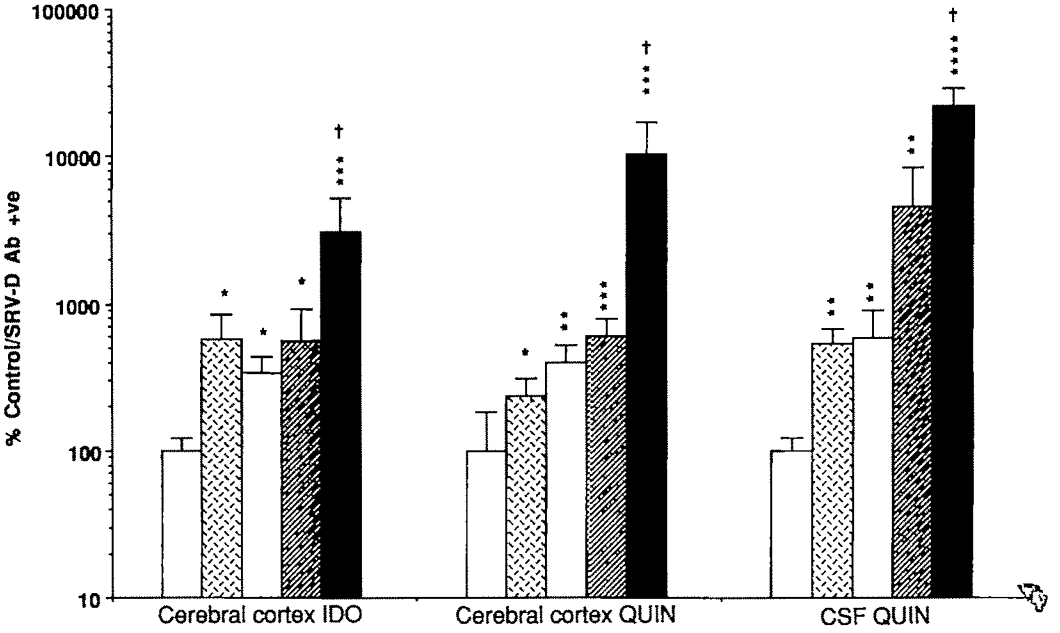

FIG. 7. Logarithmic plot of cerebral cortex IDO activity, cerebral cortex QUIN concentrations and cisternal CSF QUIN levels in macaques infected with simian type-D retrovirus SRV-D (broken hatched bars) or the SIV Combined values (mean ± 1 SEM) for macaques without retrovirus infection [control, failure to thrive and type-D antibody positive/virus negative (*see* Heyes *et al*, 1990*b*), n = 21; open bars] were cerebral cortex IDO activity, 3.91 ± 0.39 nmol/g/h; cerebral cortex QUIN, 132.2 ± 27.7 pmol/g and CSF QUIN, 39 ± 8.5. All macaques had higher brain QUIN concentrations than CSF. Type-D retrovirus positive macaques (n = 9) had no histopathological cellular infiltrates but class II expression was increased Simian immunodeficiency virus infected macaques are classified as having either no inflammatory lesions in the brain (n = 12; stippled bars), inflammatory responses in subcortical areas or the meninges (n = 3; hatched bars) or inflammatory responses in the cerebral cortex (n = 10; solid bars) $^{*}P < 0.05$, $^{**}P < 0.001$ and $^{***}P < 0.0001$ versus control values; $^{\dagger}P < 0.05$ versus SIV sub-cortex inflammation.

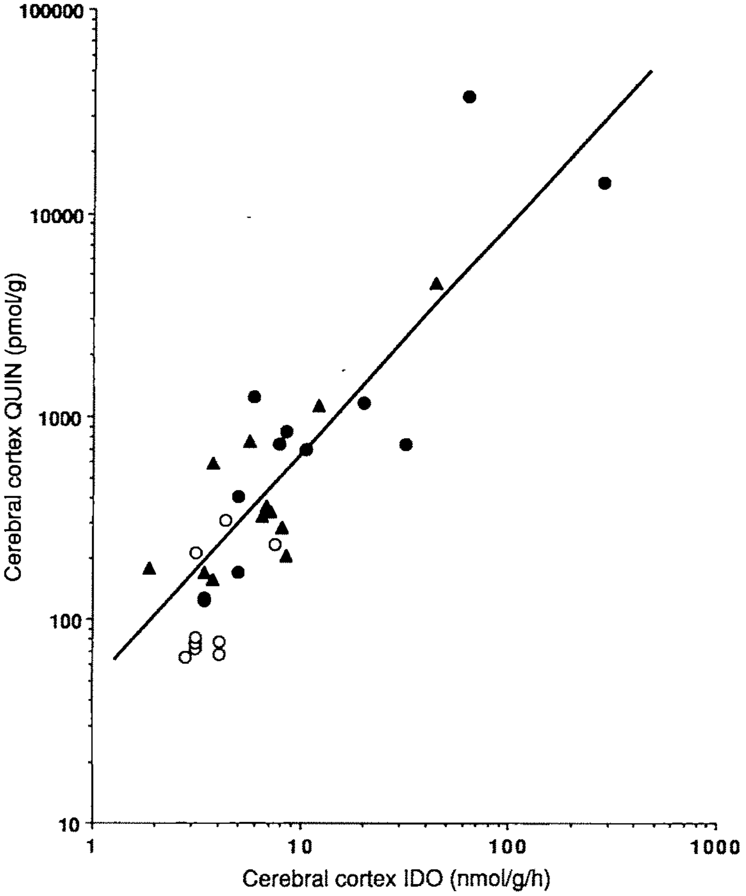

FIG 8 Significant correlation between QUIN concentrations and IDO activity in cerebral cortex of control (○), type-D retrovirus infected (▲) and SIV-infected (●) macaques studied (from Fig. 7).

Similarly, CSF neopterin levels were correlated with CSF L-KYN ($r = 0.81$, $P < 0.0001$), KYNA ($r = 0.54$, $P < 0.005$) and QUIN ($r = 0.71$, $P < 0.001$).

Lung IDO activity was increased to the same degree in the four groups of retrovirus-infected macaques (expressed as a percentage control of macaques): type-D retrovirus positive, 385±17%; SIV no CNS inflammation, 634±94%; SIV subcortex inflammation, 442±218% and SIV cortex inflammation, 319±41%. However, hepatic tryptophan-2,3-dioxygenase activity was not significantly different from controls in any retrovirus-infected group examined (type-D retrovirus positive, 122±18% of controls; SIV no CNS inflammation, 105±23%; SIV subcortex inflammation, 103±24% and SIV cortex inflammation, 96±31%). Serum L-KYN and QUIN concentrations were increased in the four groups of retrovirus-infected macaques studied to the same degree (data not shown). While the ratio of CSF : serum QUIN was <1 in control, type-D and SIV-infected macaques without evidence of brain inflammation, CSF QUIN concentrations exceeded serum levels in >21% of SIV-infected macaques with either subcortical or cortical inflammation.

DISCUSSION

In the context of the neuropathogenical potential for kynurenine pathway metabolites, we have addressed the following questions: (i) under what conditions are the levels of QUIN and neuroactive kynurenines altered in the CNS of humans? (ii) what mechanisms could be responsible for mediating such changes? (iii) what is the relationship between kynurenine pathway metabolism and the neuropathological features of the CNS? The present results demonstrate substantial and sustained increases in the levels of QUIN and neuroactive kynurenines within the CNS of patients with inflammatory neurological disease which contrast with the normal or reduced levels in patients with non-inflammatory neurodegenerative, neuropsychological or seizure disorders. The strength of this study reflects not only the large number of clinical diseases investigated, the collection of samples under stringent conditions and the use of verified assay techniques, but also the consistent increases in the concentrations of QUIN, L-KYN and KYNA across a broad spectrum of inflammatory diseases. Our previous reports of significant correlations between the magnitude of the increases in CSF QUIN and the degree of neuropsychological deficits in HIV-infected patients (Martin *et al.*, 1990; Brouwers *et al.*, 1991; Heyes *et al.*, 1991*a*) emphasizes the potential clinical significance of our present findings.

Inflammatory neurological disease

Neurological implications. Sustained increases of up to tenfold in CSF QUIN levels (Fig. 5) were observed in the early stages of HIV-infection, and neurological signs in these patients were either absent or subtle (Martin *et al.*, 1990). However, in the inflammatory disease patients who had demonstrable clinical neurological deficits, CSF and brain QUIN levels were increased between tenfold to one thousandfold (Figs 4, 7; Table 1) and exceeded the 100 nM concentrations that are toxic to certain types of neurons *in vitro* (Whetsell and Schwarcz, 1989; Giulian *et al.*, 1990). It is likely that CSF QUIN values are an index of extracellular fluid QUIN concentrations. Therefore, QUIN may contribute to the neurodegeneration that occurs in patients with certain inflammatory neurological disease by activation of *N*-methyl-D-aspartate receptors. Several other factors can affect the neurotoxicity of QUIN, including the regional distribution of *N*-methyl-D-aspartate receptors (Monaghan *et al.*, 1989), the relative sensitivity of neurons to QUIN (Perkins and Stone, 1983), the duration of QUIN exposure (Whetsell and Schwarcz, 1989), the stage of neuronal maturity (Keilhoff *et al.*, 1991) and the local concentrations of other receptor modulators, including zinc (Koh and Choi, 1988), glycine (Monaghan *et al.*, 1989) and KYNA (Foster *et al.*, 1984; Boegman *et al.*, 1990). We also do not exclude the possibility that QUIN may exert neurological effects by mechanisms independent of *N*-methyl-D-aspartate receptors, including chelation of cations. It is important to note that focal brain QUIN concentrations would substantially exceed the CSF values if QUIN was synthesized in discrete brain regions, and particularly if production was restricted to certain cell types (*see below*). Indeed, the highest cerebral cortex QUIN concentrations were noted in the macaques with local inflammatory lesions and concentrations in brain parenchyma exceeded CSF concentrations (Fig. 8). In a separate study, SIV-infected macaques with the largest increases in CSF QUIN concentrations developed brain atrophy (Heyes *et al.*, 1992*a*). Furthermore, in the patient with herpes encephalitis (Fig. 6), the highest QUIN concentrations occurred in the regions where the virus localizes, and where both neurodegeneration and inflammation are most pronounced, namely the temporal lobes (grey matter, 16 464 nM; white matter 11 495 nM) as well as the hippocampus (9579 nM). It is of note that the hippocampus is an area rich in *N*-methyl-D-aspartate receptors (Cotman *et al.*, 1988; Monaghan *et al.*, 1989; Keihloff *et al.*, 1991) and is very sensitive to the neurotoxic effects of QUIN (Schwarcz *et al.*, 1983).

Although KYNA attenuates the excitotoxic effects of QUIN when co-infused with QUIN in at least equimolar concentrations (Foster *et al.*, 1984; Boegman *et al.*, 1990), CSF QUIN concentrations exceeded CSF KYNA levels in control subjects by approximately sevenfold, and the elevations in CSF QUIN were greater than the increases in CSF KYNA (Figs 4–6). Clearly, the ratio of QUIN : KYNA favours neurotoxicity. Increases in the CSF QUIN : KYNA ratio occurs in other circumstances of immune activation (Heyes and Lackner, 1990; Heyes *et al.*, 1990*b*, 1992*a*; Halperin and Heyes, 1992). Quinolinic acid and KYNA could also produce neurological deficits by non-cytolytic mechanisms, by competing with other endogenous excitatory amino acid receptor modulators, such as glutamate, or down-regulating *N*-methyl-D-aspartate receptors (Peterson *et al.*, 1990), a response that may actually protect against the neurodegenerative effects of QUIN. While neurodegenerative changes would not be expected to be reversible, non-cytolytic disruption of neuronal activity may be reversed if QUIN and KYNA concentrations were normalized. The improvements in neuropsychological performance in conjunction with reductions in CSF QUIN following azidothymidine treatment of HIV-infected patients may be consistent with this notion (Brouwers *et al.*, 1991; Heyes *et al.*, 1991*a*).

It is of note that the clinical manifestations of QUIN-induced lesions would reflect the function of the brain region that was damaged. For example, lesions of the hippocampus would produce different neurological deficits compared with damage to the striatum. *N*-Methyl-D-aspartate receptors mediate a broad range of neurological functions including excitatory amino acid neurotransmission, synaptic plasticity, synaptogenesis, differentiation, learning and memory (Cotman *et al.*, 1988; Hunt and Patel, 1990). Therefore we propose that QUIN and KYNA may act as final common mediators of a broad spectrum of neurological deficits, including motor, cognitive or behavioural abnormalities.

Mechanisms involved in increasing CNS kynurenine pathway metabolites. A model of the factors which influence the concentrations of kynurenine pathway metabolites within the blood and CNS is presented in Fig. 9. The present and previous results suggest that the increases in CNS kynurenines in the inflammatory disease patients were not dependent upon increased permeability of the blood-brain barrier (Heyes *et al.*, 1991*a*, 1992*a*; Halperin and Heyes, 1992), which normally has a low permeability to QUIN and KYNA (Fukui *et al.*, 1991), because both CSF protein and albumin concentrations as well as the CSF : serum albumin ratio were normal in the majority of the inflammatory disease patients studied. Furthermore, there were no correlations between these indices of blood-brain barrier integrity and the concentrations of QUIN, KYNA or L-KYN in the CSF (Tables 2, 3). Cerebrospinal fluid QUIN concentrations exceeded blood levels in 21% of the macaques with post-mortem inflammatory CNS lesions, clearly supporting intrathecal synthesis of QUIN (*see also* Heyes *et al.*, 1991*a*, 1992*a*).

The results show proportional increases in QUIN, KYNA and L-KYN concentrations in the CNS that were significantly correlated to cerebral cortex IDO activity (Fig. 8).

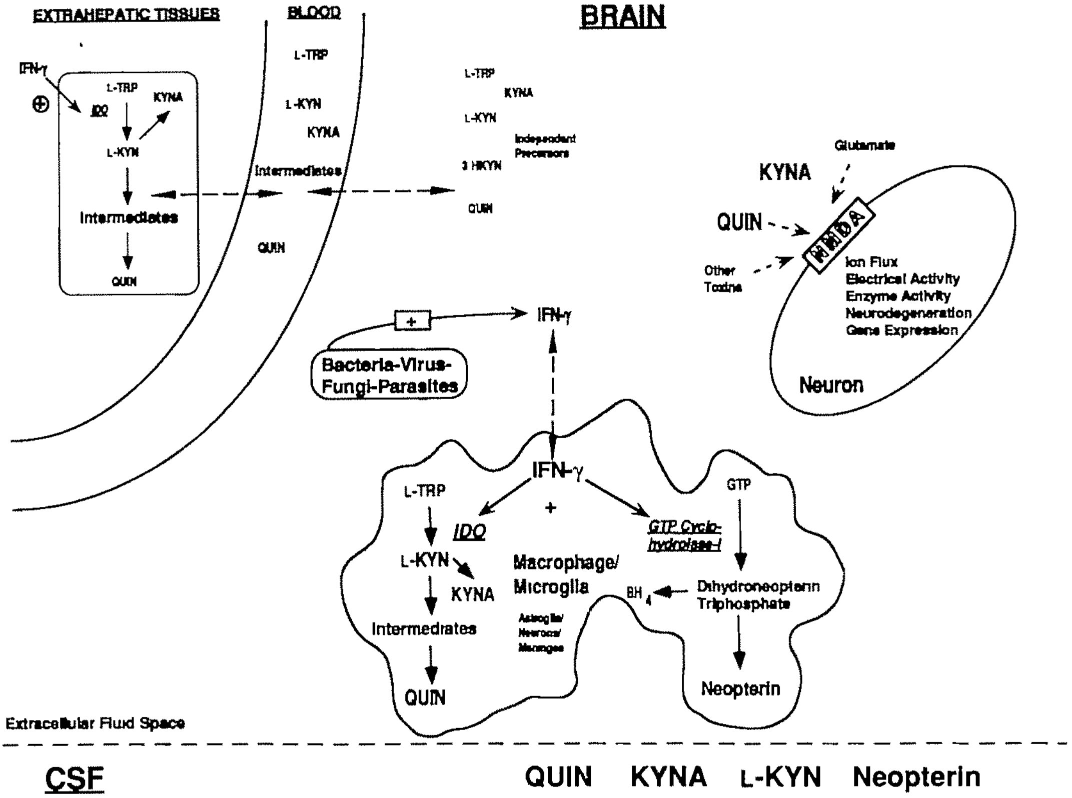

FIG. 9. Model of kynurenine pathway metabolism in inflammatory diseases. In brain, the presence of bacteria, virus, fungi, parasites or autoimmune processes results in the release of cytokines including those which activate indoleamine-2,3-dioxygenase (IDO). Increases in IDO activity accelerate the degradation of L-tryptophan (L-TRP) to neuroactive kynurenines including the excitotoxin, quinolinic acid (QUIN) and the antagonist of excitatory amino acid receptors, kynurenic acid (KYNA). Such metabolic conversion may occur in several cell types within the CNS, including macrophages (Heyes *et al.*, 1992*b*) In the case of systemic immune stimulation, cytokines or precursors of neuroactive kynurenines may enter the brain from the blood, particularly where the blood-brain barrier is impaired. The presence of QUIN, KYNA and other toxins may influence the activity of *N*-methyl-D-aspartate (NMDA) receptors and result in neurological deficits and neurodegeneration.

The highest IDO activity in the CNS occurred in macaques with inflammatory lesions, including macrophages infiltrates into the brain parenchyma and meninges although increases did occur in macaques without obvious inflammatory lesions. Induction of IDO in human macrophages by interferon-γ results in accelerated conversion of [$^{13}C_6$]L-tryptophan to [$^{13}C_6$]QUIN (Heyes *et al.*, 1992*b*), as well as the production of L-KYN, anthranilic acid and 3-hydroxyanthranilic acid (Werner *et al.*, 1987). This latter metabolite is readily converted to QUIN in brain (Heyes *et al.*, 1988*a*). Notably, the concentration of QUIN that was achieved in macrophage/monocyte cultures following stimulation by interferon-γ, exceeded 25 000 nM. Therefore, inflammatory cell infiltrates in the brain parenchyma and meninges likely contain IDO and other kynurenine pathway enzymes, and are an important source of QUIN. Conversion of [$^{13}C_6$]L-tryptophan to [$^{13}C_6$]QUIN has also been demonstrated within the CNS of macaques infected with SIV

(Heyes *et al.*, 1992*a*), which indicates that changes in the activity of IDO may have a significant impact on QUIN formation. The production of QUIN may also be facilitated by increased activity of 3-hydroxyanthranilate-3,4-dioxygenase, the formation enzyme for QUIN, secondary to astrogliosis (Okuno *et al.*, 1987; Speciale *et al.*, 1987; Schwarcz *et al.*, 1988*a*). However, such increases in 3-hydroxyanthranilate-3,4-dioxygenase alone do not result in increased brain or CSF QUIN concentrations in patients with Huntington's disease. Therefore, an increase in the production of 3-hydroxyanthranilic acid is needed for increased activity of 3-hydroxyanthranilate-3,4-dioxygenase to have an impact on the rate of QUIN production. The presence of macrophages are clearly one circumstance where this can occur. Accumulation of QUIN may reflect the relatively low activity of quinolinic acid phosphoribosyl transferase in brain (Foster *et al.*, 1985).

The increases in CSF QUIN, KYNA and L-KYN were proportional to the degree of inflammatory responses in the CNS, as indicated by their correlations to CSF IgG, neopterin and pleocytosis (Tables 2, 3). Neopterin is produced following activation of GTP cyclohydrolase I by interferon-γ (Fuchs *et al.*, 1989; Fig. 9). Therefore, IDO induction within the CNS may be attributable to the effects of interferon-γ. In this context, systemic administration of interferon-γ to mice replicates many of the key metabolic features noted in the patients with inflammatory disease (Saito *et al.*, 1991*b*). Also, the stimulatory effects of pokeweed mitogen on IDO activity and kynurenine pathway metabolism are attenuated by co-administration of a specific anti-mouse interferon-γ antibody (Saito *et al.*, 1992). The small increases in CSF QUIN and neopterin, as well as the development of statistically significant inter-correlations between CSF L-KYN, QUIN and neopterin in patients with chronic fatigue syndrome, also suggests the presence of immune stimulation within the CNS. This is compatible with recent data suggesting that immune stimulation may be a hallmark disturbance in immune function in patients with chronic fatigue syndrome (Gupta and Vayuvegula, 1991).

Other factors may influence kynurenine pathway metabolite concentrations within the CNS. Although macrophage and other inflammatory cell infiltrates are a likely source of QUIN, KYNA and L-KYN, a breakdown of the blood-brain barrier may be important in some instances, such as acute head injury. However, while head injury and cerebral ischaemia are not normally considered 'inflammatory diseases', macrophage infiltrates do occur following trauma in conjunction with neurodegeneration (Cervos-Navarro and Lafuente, 1991). The increase in CSF QUIN in the two patients with head injury in the present study were also accompanied by increases in CSF L-KYN and KYNA levels, responses consistent with IDO activation. The increases in CSF QUIN levels in children with glutaric aciduria type-1 are consistent with the deficiency in glutaryl-CoA dehydrogenase, as well as the infections that were present or suspected in these children (Heyes, 1987). Systemically synthesized metabolites that are produced in response to IDO induction in systemic tissues may also enter the CNS from the blood for subsequent metabolism (fig. 11 in Gal and Sherman, 1980; Takikawa *et al.*, 1986; Heyes *et al.*, 1988*b*, 1989; Saito *et al.*, 1991*b*), such as septicaemia and retrovirus infection where both blood L-kynurenine and QUIN levels are increased (Heyes and Lackner, 1990; Heyes *et al.*, 1991*a*, 1992*a*).

The present and previous results do not support a role for hepatic tryptophan-2,3-dioxygenase in the systemic or CNS responses (Takikawa *et al.*, 1986; Heyes *et al.*, 1988*b*, 1989; Saito *et al.*, 1991*a*,*b*), because hepatic tryptophan-2,3-dioxygenase activity was not altered in either the type-D retrovirus or SIV-infected macaques. Furthermore, intracerebral synthesis of QUIN is indicated in at least some patients and macaques of the present and previous studies, as CSF and brain QUIN concentrations exceeded blood levels in some cases (Heyes *et al.*, 1991*a*, 1992*a*).

An important question to consider is why IDO activity is induced and why neuroactive kynurenine pathway metabolites are synthesized in inflammatory disease. Interferon-γ has strong anti-microbial, anti-proliferative and anti-tumour effects, and induction of IDO by interferon-γ, with concomitant depletion of L-tryptophan, has been proposed as a possible mechanism to limit replication of intracellular parasites (*see* Taylor and Feng, 1991). Reductions in CSF L-tryptophan concentrations did occur in the more severely affected patients and macaques, as noted previously (Werner *et al.*, 1988; Larsson *et al.*, 1989; Fuchs *et al.*, 1990; Heyes *et al.*, 1990*b*). The reactions catalysed by IDO and 3-hydroxyanthranilate-3,4-dioxygenase also absorb oxygen free radicals. Picolinic acid, which should also be produced following IDO induction, is a co-factor in macrophage activation (Varesio *et al.*, 1990). Therefore, induction of IDO could conceivably be of benefit, despite the synthesis of neuroactive kynurenine pathway metabolites. Conversely, depletion of L-tryptophan may be detrimental, including impairments in protein synthesis and reduced synthesis of indoleamines with concomitant neurological deficits including depression. There is evidence that reductions in serotonergic activity occur in retrovirus infections (Larsson *et al.*, 1989; Heyes *et al.*, 1990*b*). Increases in systemic metabolites may also have detrimental consequences including impaired gluconeogenesis and alterations in cardiac contractility (Snoke *et al.*, 1971; Heyes and Lackner, 1990; Beskid *et al.*, 1991). Clearly, further studies to discriminate beneficial versus detrimental effects are warranted.

Non-inflammatory neurological disease

A large body of data from experimental animals has indirectly implicated QUIN in the pathogenesis of chronic neurodegenerative disorders (Schwarcz *et al.*, 1983, 1984, 1988*b*; Moroni *et al.*, 1986*a*; Heyes, 1987; Whetsell and Schwarcz, 1989; Heyes *et al.*, 1990*c*). Particular interest has focused on both Huntington's disease and Alzheimer's disease because of the similarities between QUIN-induced lesions in rats and the feature of post-mortem human brains with these diseases (Schwarcz *et al.*, 1983, 1988*a*; Beal *et al.*, 1986; Young *et al.*, 1988; Whetsell and Schwarcz, 1989; Boegman *et al.*, 1990). The present and previous results do not support this hypothesis, because both post-mortem regional brain and CSF QUIN concentrations were normal or reduced in both Huntington's disease and Alzheimer's disease (Moroni *et al.*, 1986*b*; Reynolds *et al.*, 1988; Schwarcz *et al.*, 1988*b*; Mouradian *et al.*, 1989). Cerebrospinal fluid levels were not elevated during the early phases of disease, when neurodegeneration was occurring, and symptoms continued to worsen even though CSF QUIN levels remained within or below the normal range. Furthermore, despite significant increases in QUIN concentrations in patients and macaques with inflammatory diseases, the clinical features of either Huntington's disease or Alzheimer's disease did not develop. Clearly, the quinolinic acid and excitotoxic hypothesis of chronic non-inflammatory neurodegenerative diseases requires modification.

The concentrations of KYNA were lower in the CSF of patients with Huntington's disease (Fig. 3), as noted previously (Beal *et al.*, 1990), and may be viewed as promoting excitotoxicity (Foster *et al.*, 1984). However, KYNA levels in the putamen itself are not significantly different from controls (Connick *et al.*, 1989; Beal *et al.*, 1990), and there is a report that cerebral cortex KYNA levels are actually increased in Huntington's disease (Connick *et al.*, 1989). The reductions in CSF KYNA concentrations in Huntington's disease may be secondary to the reduced availability of L-KYN in the CNS (Fig. 4). Alternatively, the reductions in the CSF concentrations of QUIN and KYNA may be secondary to brain atrophy and expansion of the CSF space. The levels of KYNA in CSF was also lower in patients with Alzheimer's disease, although the significance of this finding with respect to neurotoxicity is unclear.

Conclusions

We conclude that the available data do not support a role for QUIN in the aetiology of Huntington's disease or Alzheimer's disease. This conclusion is anti-thetical to commonly held assumptions. In contrast, substantial increases in the concentrations of QUIN, KYNA and L-KYN occur in the CNS of patients with a broad spectrum of inflammatory diseases. Further, the rate of substrate flux through the kynurenine pathway appears to be dependent on activation of IDO within the CNS. In view of the established neuropathological effects of certain kynurenine pathway metabolites and the correlations between CSF QUIN levels and quantitative measures of neuropsychological deficits in patients infected with HIV-1 (Martin *et al.*, 1990; Brouwers *et al.*, 1991; Heyes *et al.*, 1991*a*), we propose that the production of these metabolites within the CNS may be of clinical significance. Quinolinic acid, KYNA and other neuroactive kynurenine pathway metabolites may be important common mediators of neurological dysfunction in a broad spectrum of diseases associated with endogenous and exogenous stimulation of the immune system. If this hypothesis is correct, then strategies to reduce the synthesis of neuroactive kynurenine pathway metabolites, or attenuate their effects, offer new approaches to therapy of neurological deficits associated with inflammatory diseases.

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FAMILIAL AMYLOID POLYNEUROPATHY ASSOCIATED WITH THE TRANSTHYRETIN CYS114 GENE IN A JAPANESE KINDRED

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SUMMARY

A Japanese kindred with dominantly inherited amyloid polyneuropathy, commonly called familial amyloid polyneuropathy (FAP), has been identified. Amyloid protein was transthyretin (TTR) related and the patients were heterozygous for the mutant gene encoding TTR with a single amino acid substitution of cysteine for tyrosine at position 114. This family originated in Nagasaki Prefecture, Japan, and 12 of the 36 known members of six generations have been affected. The initial symptoms occurred in their thirties with the cardinal features of polyneuropathy, vitreous opacities and cardiac disease. Sensory neuropathy was severe in the lower limbs. Autonomic disturbances, especially postural hypotension, were the most debilitating to the patients. Amyloid deposits were detected widely in most organs except for the central nervous system. The duration from the onset of the disease to death was within 10 yrs. Heart failure caused by heavy amyloid deposits was the most common cause of sudden death.

INTRODUCTION

Among familial systemic amyloidoses, only type I familial amyloid polyneuropathy (FAP) was known to exist in Japan in the past two decades (Araki *et al.*, 1968; Kito *et al.*, 1980). It is clinicopathologically identical with the disease first found in Portugal in 1952 (Andrade) and subsequently in many countries. The molecular basis of the disease is a single amino acid substitution of methionine for valine at position 30 of the transthyretin (TTR) molecule, $\mathrm{TTR}^{\mathrm{Met30}}$ (Dwulet and Benson, 1983, 1984; Tawara *et al.*, 1983; Saraiva *et al.*, 1984).

In 1990, we identified three additional mutations in the TTR gene from three different Japanese families with amyloid polyneuropathy, $\mathrm{TTR}^{\mathrm{Cys114}}$, $\mathrm{TTR}^{\mathrm{Gly42}}$ and $\mathrm{TTR}^{\mathrm{Arg50}}$ (Ueno *et al.*, 1990*a,b*). Subsequently, we found three more mutants, $\mathrm{TTR}^{\mathrm{Arg58}}$ (Saeki *et al.*, 1991), $\mathrm{TTR}^{\mathrm{Ile50}}$ and $\mathrm{TTR}^{\mathrm{Leu30}}$ (unpublished data) in another three families, thereby giving evidence for the molecular heterogeneity of the Japanese FAP. The one

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with a substitution of cysteine for tyrosine at position 114 (TTR^{Cys114}) was found in the largest of the six families. We describe the clinicopathologic features of patients in this kindred.

PATIENTS

The present family originated in Kunimi, Nagasaki Prefecture. [It is noteworthy that two kindreds with different mutations, TTR^{Met30} in Arao (Kumamoto Prefecture) and TTR^{Cys114} in Kunimi, were identified within a relatively small area.] The family history through six generations revealed 12 affected members with autosomal dominant inheritance (Fig. 1). The family register showed that the proband's great-grandmother (I-2) was born in 1835 and died at the age of 88, but no detailed information is available.

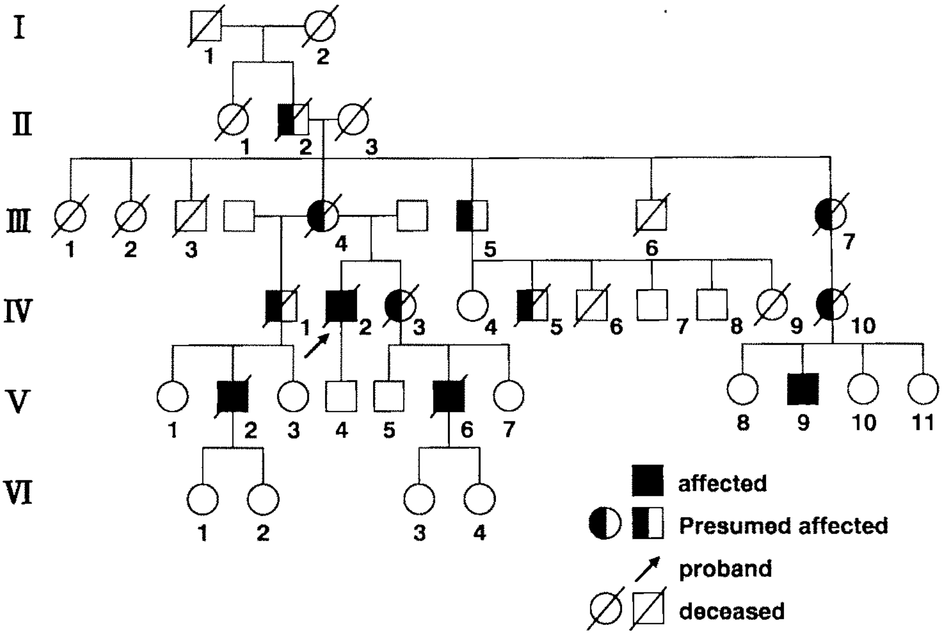

FIG. 1. The pedigree of the family with FAP associated with the TTR^{Cys114} gene

In 1937 the proband's grandfather (II-2) moved from Kunimi to Osaka, where his descendants have lived. The grandfather reportedly suffered from visual cloudiness, fainting on standing and intractable diarrhoea. The proband's mother (III-4) had visual cloudiness, fainting and difficulty with urination. She died suddenly at the age of 50 yrs. The proband's brother (IV-1) suffered from visual cloudiness, marked weight loss and difficulty in urination. He died at the age of 49 yrs. Five other family members (III-5, 7; IV-3, 5, 10) were reportedly affected by this disease. Dysaesthesiae in the lower limbs, bowel and sphincter disturbances, and dizziness on standing occurred in their thirties. Three of them had visual cloudiness. All five died in their early forties. In 1970 the proband (IV-2) first visited Osaka University Hospital and we have examined three affected relatives (V-2, 6, 9) since then. The clinical and laboratory features are summarized in Table 1.

TABLE 1 SUMMARY OF THE CLINICAL AND LABORATORY FINDINGS

	Case IV-2	*Case V-6*	*Case V-2*	*Case V-9*
Age of onset, sex	39, M	34, M	31, M	34, M
Age at death	46	40	38	Alive
Symtom at onset	Cloudy vision	Dysuria	Cold foot	Dizziness
Vitreous opacity*	+	+	+	+
Neuropathy** of upper/lower limb	+/+++	+/+++	++/+++	+/+++
Nerve conduction velocity (m/s)				
Median nerve				
MCV (57.5±4.9)	48.5	51.3	48.8	50.6
SCV (61.9±4.2)	60.1	60.3	40.9	55.5
Posterior tibial nerve				
MCV (48.5±3.6)	43.1	42.0	36.9	34.5
Sural nerve	No response	No response	No response	No response
Electromyogram	Polyphasic	Polyphasic	Polyphasic	Polyphasic
Autonomic failure*	+	+	+	+
Cardiomegaly*	+	+	+	−
Electrocardiogram	Low voltage, AF Sinus arrhythmia	Ischaemic Sinus arrhythmia	PAC Ischaemic	PAC, PVC
Sural nerve amyloid*	−	+	+	+

*+ = present, − = absent, **+ = mild, ++ = moderate; +++ = severe; MCV = motor nerve conduction velocity, SCV = sensory nerve conduction velocity, AF = atrial fibrillation, PAC = premature atrial contraction, PVC = premature ventricular contraction.

Case IV-2

This male proband developed visual cloudiness and then impotence, cold feet and orthostatic dizziness at the age of 39 yrs. Three years later, he began to experience vomiting, urinary incontinence, chronic constipation and muscular weakness in the lower limbs. On admission at the age of 42 yrs, his blood pressure was 132/90 lying and 94/64 standing, with a constant pulse rate of 82. Vitreous opacity was present in the right eye Cardiomegaly was absent. The cranial nerves and upper limbs were unremarkable. He had moderately atrophic muscles in the distal part of the lower limbs. There were decreased light-touch pain and thermal senses in the lower limbs, more distally, while position and vibratory senses were slightly impaired below the ankles The results of routine laboratory tests were normal. Cerebrospinal fluid (CSF) was normal except for increased protein (98 mg/dl). Valsalva manoeuvre produced no decrease in the heart rate. A cold test showed no increase in the heart rate. Noradrenaline infusion raised blood pressure from 118/78 to 180/122 and the heart rate from 84 to 140. Intravenous atropine infusion resulted in no increase in the heart rate. Sweating was markedly reduced on the surface of the legs and back. Cystometry revealed a neurogenic atonic bladder. Sural nerve biopsy showed depletion of nerve fibres, but Congo red staining was negative.

Over the next 3 yrs, proprioception became markedly decreased below the knee and lost in the toes. He worked as a booking clerk until his sudden death at the age of 46 yrs. A limited autopsy elsewhere revealed gross cardiomegaly (500 g), but no myocardial infarction was found

Case V-6

This case was a nephew of the proband. He began to have difficulty in urination and became sexually impotent at the age of 34 yrs. Three years later, he experienced the first attack of syncope on standing, developed cold feet and burnt his leg without feeling pain. He also developed visual cloudiness in his left eye and chronic constipation. On admission at the age of 38 yrs, his blood pressure was 162/100 lying and 50/0 standing, with a constant pulse rate of 78. Vitreous opacity was present in the left eye. There was no abnormality in the upper limbs but moderately atrophic muscles were present in the distal part of lower limbs. Light-touch, pain and thermal senses were moderately impaired in the lower limbs, more distally but vibratory and position senses were normal. Valsalva manoeuvre produced little change in the heart rate. Sweating was markedly diminished on the trunk and lower limbs. Cerebrospinal fluid showed a total protein of 338 mg/dl at the age of 38 yrs (Table 2). Chest X-ray revealed cardiomegaly. Sural nerve biopsy showed depletion of both myelinated and unmyelinated fibres, axonal degeneration and small deposits of Congo red-positive substances. He was able to walk with mechanical assistance until his sudden death at the age of 40 yrs.

TABLE 2 SERUM AND CSF PROTEIN PROFILES OF A PATIENT (CASE V-6)

After onset (mths)	*Serum*			*CSF*				
	Albumin	*IgG*	*TTR**	*Total protein*	*Albumin*	*IgG*	*TTR***	*TTR****
24	1320	230	2.2	149	117	14.9	2.3 (0.2)	(2.1)
36				178				
37	884	180	1.4	197	161	24.1	1.7 (0.4)	(1.3)
41				221				
47	836	170	1.2	338	265	33.8	2.0 (0.6)	(1.4)

Each value is expressed as mg/dl. *Normal serum range = 21−43 mg/dl; **blood-CSF barrier-dependent TTR: [albumin (CSF)]/[albumin (serum)] × TTR (serum), ***blood-CSF barrier-independent TTR was calculated by substraction of the (**) from the measured TTR concentration in CSF.

At post-mortem, widespread amyloid deposits were found in the blood vessel walls and perivascular areas in virtually all organs except in the parenchyma of the brain and spinal cord. The leptomeninges of the spinal cord were thickened by massive amyloid deposits. Cardiac weight was 480 g and there was concentric hypertrophy of the myocardium with amyloid deposits (Fig. 2A,B,C). Amyloid was heavily deposited in the mucosa and submucosa of the stomach and small intestine. In the kidney, the perivascular space contained only slight amyloid deposits (Fig. 3A,B). In the autonomic nerves in the kidney, amyloid deposits were observed within the perineurium and epineurium (Fig. 4A,B).

Case V-2

This case was also a nephew of the proband. He developed coldness of the legs and intermittent shooting pain in the posterior thighs at the age of 31 yrs and developed impotence, orthostatic dizziness and alternating diarrhoea and constipation with incontinence by the age of 35 yrs. On examination, he had orthostatic hypotension, slight muscle atrophy and decreased pain and thermal sensation distally in the legs. Vibratory and position senses were severely impaired only in the toes. The sural nerve and rectal biopsies showed slight amyloid deposits. There was decreased sweating in the lower limbs and autonomic function tests showed widespread disturbance of the autonomic nervous system (Table 3). During the next year, his symptoms worsened and he developed vitreous opacities and dysaesthesiae in the hands. The serum TTR level was low (8.5 mg/dl, normal range: 21−43 mg/dl) and CSF protein was 71 mg/dl. He died suddenly at the age of 38 yrs. At autopsy, amyloid deposits were observed in the perivascular space of every organ studied, but not in the spinal cord. The brain was not examined. The sciatic nerve contained amyloid deposits which were also strained with anti-TTR serum (Fig. 5A,B). In the kidney, amyloid deposits were found only in the perivascular space.

Case V-9

This case is a son of the proband's cousin. He noticed dizziness on standing at the age of 34 yrs, and then developed impotence, difficulty in urination, muscle weakness and dysaesthesiae in the thighs. At the age of 36 yrs, the examination revealed orthostatic hypotension, vitreous opacities, muscle atrophy and decreased touch and pain sensation distally in the legs. He had a clinical course similar to that of the previous three patients, and has been confined to a wheelchair since the age of 38 yrs. Sural nerve and gastric mucosa biopsies showed amyloid deposits. Laboratory findings were normal except for a low concentration of serum TTR (10 mg/dl) and elevated CSF protein (74 mg/dl). There was no elevation of the serum noradrenaline or adrenaline levels on standing. The pupils were unresponsive to tyramine but were dilated by adrenaline.

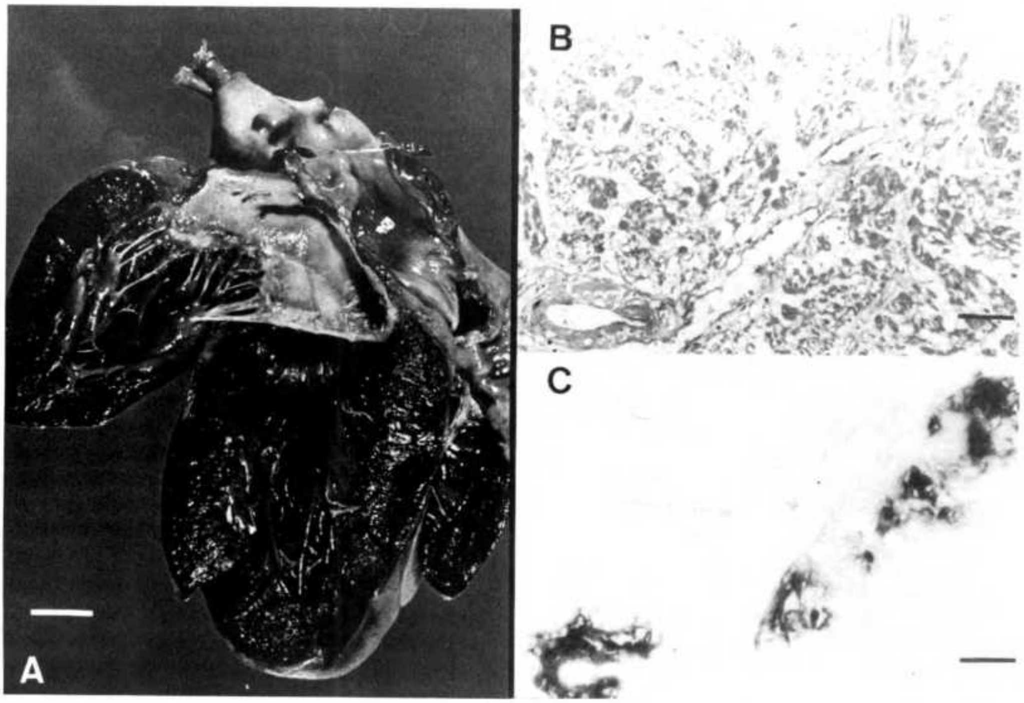

FIG. 2. A, marked hypertrophy of the left ventricular wall of the heart in *Case V-6*. Bar = 2.5 cm. B, microscopic findings in the myocardium of the same patient (haematoxylin and eosin staining); C, immunohistochemical staining with anti-TTR antibody. Bar = 50 μm.

LABORATORY FINDINGS

Immunohistochemistry for amyloid deposition

The tissue specimens were subjected to immunohistochemical staining with anti-TTR antiserum and 24 other antisera including immunoglobulin and Bence Jones protein (κ and λ chains), but amyloid deposits reacted only with anti-TTR antiserum (Figs 2, 4, 5). Amyloid fibrils, prepared from autopsied kidney tissue by the method of Costa *et al.* (1978), possessed TTR by a double immunodiffusion assay (data not shown).

Autonomic cardiovascular responses

Orthostatic hypotension without increase in the heart rate and a lack of response of the blood pressure and heart rate to cold stimulation indicated that the cardiac sympathetic nervous system was predominantly affected. Decreased secretion of adrenaline and noradrenaline in response to postural changes confirmed sympathetic disturbance. R-R interval variations with posture, Valsalva manoeuvre and at forced respiration were abnormal, indicating impairment of the parasympathetic nervous system. Intravenous noradrenaline infusion caused abnormally high blood pressure. Intravenous atropine infusion failed to induce a significant increase of the heart rate. Typical and representative data (Case V-2) are shown in Table 3.

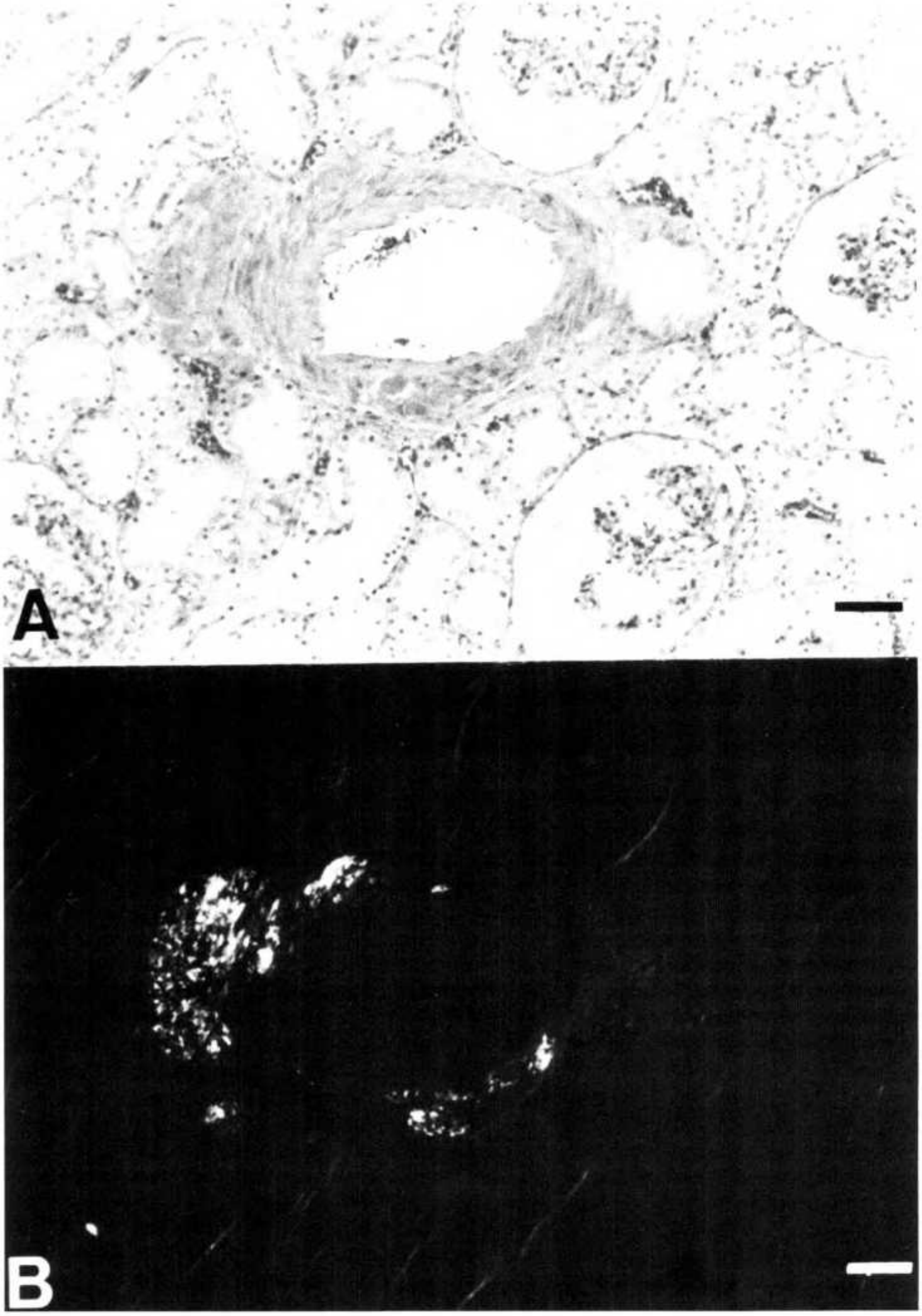

FIG. 3. Amyloid deposits in the vascular wall of the kidney from *Case V-6*. A, stained with Congo red; B, observed under a polarized light microscope. Bar = 50 μm.

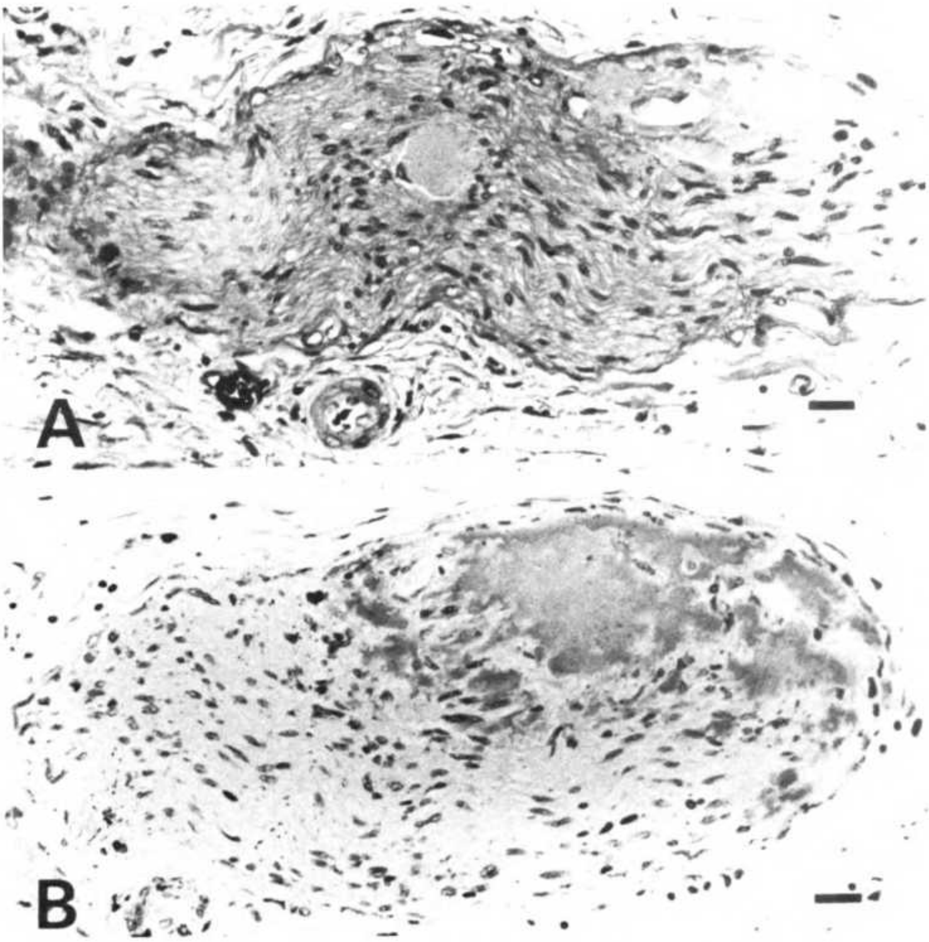

FIG. 4. Amyloid deposits in an autonomic nerve in the kidney from *Case V-6*. A, with haematoxylin and eosin staining; B, immunohistochemical staining with anti-TTR antibody. Bar = 50 μm.

Cerebrospinal fluid protein and serum TTR

Cerebrospinal fluid and sera were analysed for albumin, IgG and TTR concentrations. All three proteins were reduced in the sera, while the total CSF protein increased as the disease process advanced (Table 2). Transthyretin in the CSF can be divided into two components. One is blood-CSF (B-CSF) barrier-dependent TTR, which can be estimated from the concentration of TTR in the serum and the concentration gradient (serum/CSF) of albumin. The other is B-CSF barrier-independent TTR, which can be calculated by subtraction of the B-CSF barrier-dependent TTR from the measured TTR (Weisner and Roethig, 1983). The barrier-dependent TTR was a minor component, but it increased gradually as the disease progressed. The B-CSF barrier-independent TTR decreased in parallel to the serum TTR.

TABLE 3 CARDIOVASCULAR RESPONSE OF A PATIENT (CASE V-2)

Heart rate and blood pressure under various conditions

	Heart rate (beats/min)			*Blood pressure (mmHg)*		
	Before	*During*	*After*	*Before*	*During*	*After*
Position						
Supine	—	80	—	—	110/72	—
Sitting	—	80	—	—	68/36	—
Cold	82	82	82	111/73	119/73	105/65
Atropine (1.2 mg, i.v.)	80	80	80	120/75	121/80	120/80
Noradrenaline (0.5 μg/min i.v. for 5 min)	78	140	72	109/53	143/70	110/60

R-R interval (ms) and heart rate (beats/min) at forced respiration

	Max.	*Min.*	*Mean*	*SD*	*CV (%)*
Before					
R-R	836	779	811	12	1.5
Heart rate	77.0	71.7	73.9	1.1	—
During					
R-R	832	784	808	9	1.1
Heart rate	76.5	72.1	74.2	0.8	—

CV = coefficient of variation (normal 5.04 ± 0.56)

Catecholamine secretion

	Supine	*Sitting*
Noradrenaline*	0.19	0.19
Adrenaline**	0.02	0.02

Normal levels at supine; *noradrenaline 0.04–0.35 ng/ml; **adrenalin <0.12 ng/ml.

DNA diagnosis of the mutant TTR

We previously reported that two patients in this family (V-2, 6) were heterozygous for the TTR$^{\text{Cys114}}$ gene (Ueno *et al.*, 1990*a*). Since then, one patient (V-9) and one asymptomatic person in this family were found, by nucleotide sequence analysis to have the mutant gene. As the single base change in the TTR gene did not produce a new restriction site, restriction fragment length polymorphism (RFLP) analysis could not be used as a direct means of detecting this mutation. We used a modified oligonucleotide primer which was designed to create a new restriction site for the endonuclease Hgi AI in the gene fragments encoding a mutant allelic exon 4. Analysis of RFLP combined with polymerase chain reaction using this primer enabled us to detect the TTR$^{\text{Cys114}}$ gene (Fig. 6). We have not carried out DNA analysis in other members of this family.

DISCUSSION

The clinicopathological features of the cases presented here are characterized by early involvement of the autonomic and sensory nervous systems and carry certain similarities as well as dissimilarities with the type I FAP caused by the mutant gene encoding TTR$^{\text{Met30}}$ which has been reported from three large foci in Portugal (Andrade *et al.*,

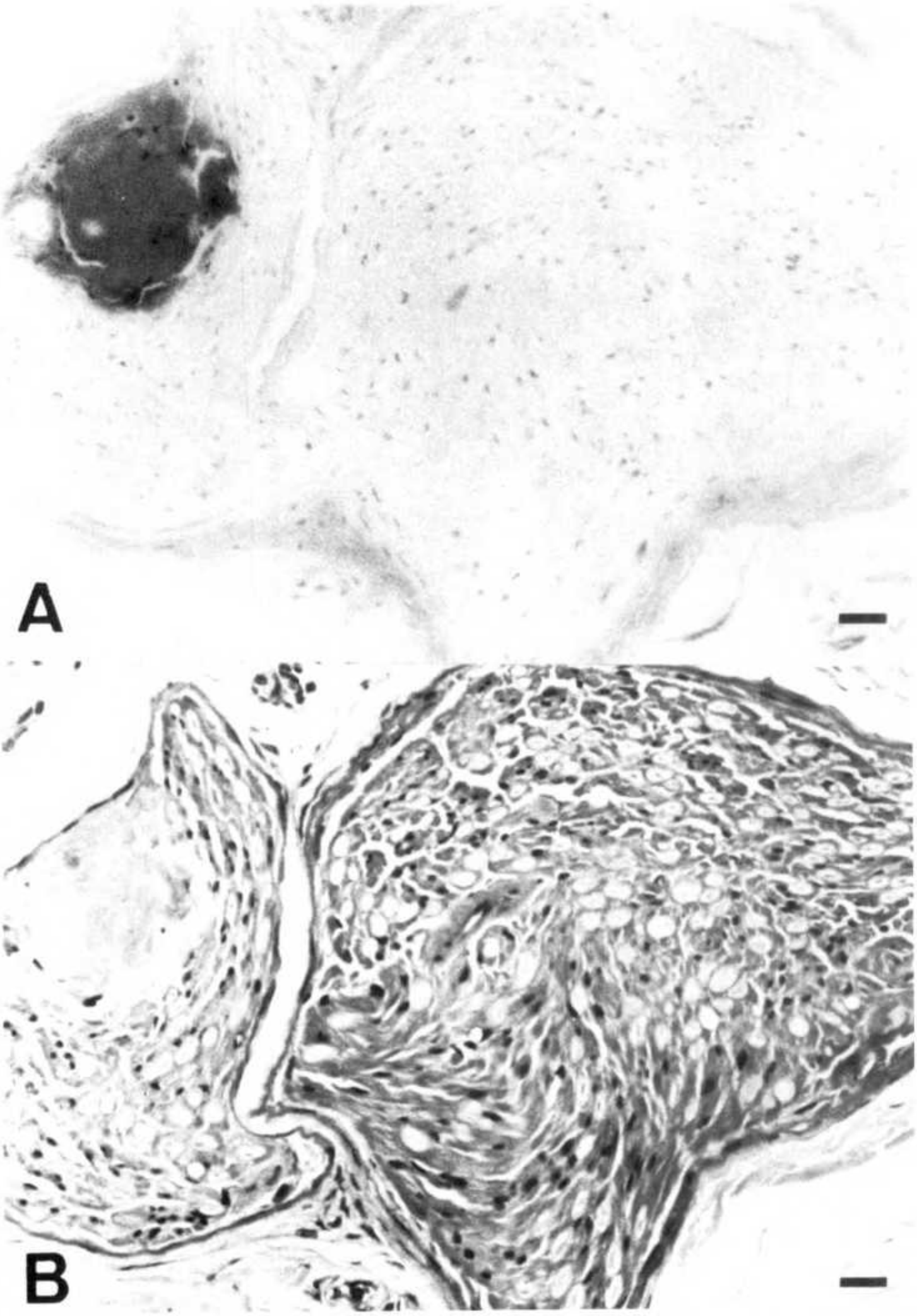

FIG. 5. The sciatic nerve from *Case V-2* showing A, immunohistochemical staining with anti-TTR and B, haematoxylin and eosin staining. Bar = 50 μm.

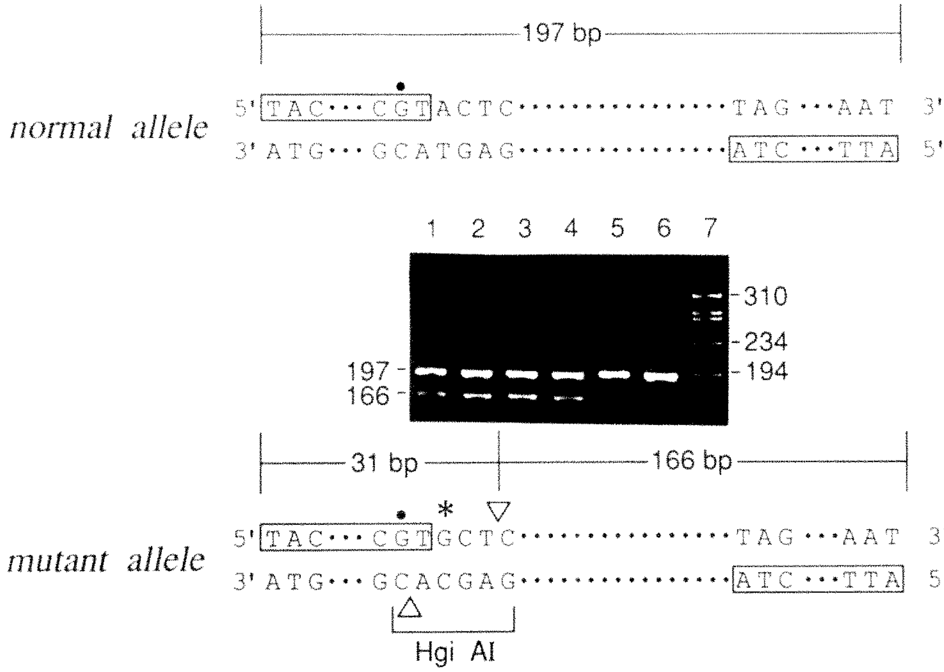
197 bp
normal allele
5' TAC ··· CGT ACTC ················ TAG ··· AAT 3'
3' ATG ··· GCATGAG ··············· ATC ··· TTA 5'
1 2 3 4 5 6 7
197
166
310
234
194
31 bp
166 bp
mutant allele
5' TAC ··· CGT GCTC ················ TAG ··· AAT 3'
3' ATG ··· GCACGAG ··············· ATC ··· TTA 5'
Hgi AI

FIG. 6. Restriction fragment length polymorphism analysis of a mutant allelic fragment containing an A to Ġ transition. The DNA sequence of the TTR gene and cDNA were based on the published data (Mita *et al.*, 1984; Tsuzuki *et al.*, 1985). A 28 nucleotide forward primer carrying a substitution of Ġ for C (5'-TACACCATTGCCGCCC-TGCTGAGCCCĠT-3') and a 22 nucleotide backward primer (5'-ATTGTCTCTGCCTGGACTTCTA-3') were designed for amplification of the two different allelic fragments (197 bp) using the polyerase chain reaction. The normal one had a single base change (C to Ġ), and the mutant one had to base changes (C to Ġ and A to Ġ). Only the latter allelic sequence could produce a new restriction site for the endonuclease Hgi AI (ĠTĠCTC), and thereby the mutant allelic segment could be digested into two fragments (166 bp and 31 bp). The gel electrophoresis showed that the three patients (lane 1, *Case V-2*; lane 2, *Case V-6*; lane 3, *Case V-9*) and one of their relatives (lane 4) were heterozygous for Hgi AI site in the TTR gene, while normal controls had no Hgi AI site (lanes 5 and 6). The size marker ϕ × 174/Hae III is shown in lane 7.

1952; Coutinho *et al.*, 1980), Japan (Araki *et al.*, 1968, 1980; Ikegawa *et al.*, 1991) and Sweden (Andersson *et al.*, 1970, 1976; Benson and Cohen, 1977).

Age of onset, clinical course and sex ratio

The mean age of onset for four patients was 34 yrs and the disease most probably started in their thirties in eight presumably affected cases, which is similar to those in the majority of type I FAP cases from Portugal (Coutinho *et al.*, 1980) and Japan (Araki *et al.*, 1980). However, the Swedish type I FAP occurred in the sixth decade (Andersson *et al.*, 1970, 1976).

Three of the four patients studied here suddenly died several years after the onset of symptoms without falling into cachexia. The eight presumably affected cases in the present family probably also died within 10 yrs of the onset of symptoms. On the other hand, the patients with type I FAP from Portugal, Japan and Sweden were frequently emaciated, confined to bed and died within 10–15 yrs, although some patients lived for more than 30 yrs after the onset of symptoms.

Since FAP presented here and type I FAP are transmitted by the autosomal dominant mode, it is expected to affect both sexes equally. However, the proportion of men to women was 2:1 both in our family with the TTR$^{\mathrm{Cys114}}$ gene and in the Swedish group with the TTR$^{\mathrm{Met30}}$ gene (Andersson *et al.*, 1976). It is known that the disease tends to manifest earlier in men than in women in the Japanese and Portuguese groups with the TTR$^{\mathrm{Met30}}$ gene (Coutinho *et al.*, 1980; Kito *et al.*, 1980). These findings suggest that there may be some sex-related factors which accelerate amyloid deposition.

Initial symptoms

Although the initial symptoms were different, the four patients studied here commonly developed both sensory and autonomic disturbances within 3 yrs after the onset. One-fifth of the Portuguese cases with type I FAP had sensory neuropathy of the lower limbs which was followed by autonomic dysfunction, while dysautonomia preceded the sensory symptoms in a quarter of the cases (Andrade, 1952). The initial symptoms in 50% of the cases with Japanese type I FAP in Kumamoto (Ikegawa *et al.*, 1991) were sensory disturbances in lower extremities.

The four patients studied here and six other cases in the present family had visual cloudiness due to vitreous opacities at an early stage. Vitreous opacities caused by amyloid deposits were reported in patients with hereditary amyloid polyneuropathy (Kaufman, 1958; Kaufman and Thomas, 1959) and were seen in the advanced Portuguese cases (Coutinho *et al.*, 1980), but not in the 375 patients in the Japanese series of type I FAP (Araki *et al.*, 1980). The prevalence of vitreous opacities in the Swedish type I FAP patients was about 10% (Sandgren *et al.*, 1990). The presence of vitreous opacities is one of the cardinal manifestations in three other kindreds: the Jewish type with TTR$^{\mathrm{Ile33}}$ (Pras *et al.*, 1983; Nakazato *et al.*, 1984); the type II FAP with TTR$^{\mathrm{Ser84}}$ (Rukavina *et al.*, 1956; Nichols *et al.*, 1989); the Italian FAP cases with TTR$^{\mathrm{Ala49}}$ (Salvi *et al.*, 1991).

Peripheral nerve involvement

In our patients, sensory impairment began in the distal part of the lower limbs and progressed in an ascending fashion. It was mild in the upper limbs even in the advanced stage. Severe impairment of temperature and pain sensations developed at the early stage, but vibratory and position senses were far less impaired even at the advanced stage. This pattern has commonly occurred in type I FAP. It has been suggested that preferential loss of unmyelinated and small myelinated axons correlated with the selective impairment of pain and temperature sensations as well as autonomic function (Dyck and Lambert, 1969; Thomas and King, 1974).

Lumbar pain, Lasègue's sign and segmental sensory loss appeared in our patients at an early stage. These signs and symptoms suggested the involvement of the proximal part of peripheral nerves. In fact, the post-mortem examination showed massive amyloid deposits in the proximal portion of the sciatic nerve even in the cases with minimal deposits in the sural nerve. Hanyu *et al.* (1989) reported heavy amyloid deposition in the proximal portion of the sciatic nerve in autopsied cases of type I FAP, but amyloid deposition was scanty in the sural nerve in spite of the total loss of myelinated nerve fibres. Sobue *et al.* (1990) also observed prominent amyloid deposits in the dorsal root ganglia, sympathetic ganglia and the most proximal part of the nerve fibres. All these findings support the notion that amyloid deposits in the most proximal portion of the nerve trunk are important in the pathogenesis of peripheral neuropathy in FAP and may be the cause of occasional failure to detect amyloid deposits in the sural nerve as we experienced in Case IV-2.

Motor function was affected much less than the autonomic and sensory functions in our patients. Conduction velocities of the motor nerves were only slightly reduced even in the absence of evoked responses in the sensory nerves. Motor nerve function was also better preserved in type I FAP in comparison to sensory nerve function. One possible explanation is the difference in the degree of neural sprouting, since the axonal sprouts were not prominent in the dorsal roots in spite of the severe fibre loss, while they were significant in the ventral spinal roots (Sobue *et al.*, 1990).

The mechanism for precipitation of variant TTR in the endoneurial space and its relation to nerve fibre generation is uncertain. Andrade (1952) reported that in type I FAP neuronal damage preceded amyloid deposition, suggesting that neuropathy was due to metabolic derangement. However, Sobue *et al.* (1990) demonstrated a parallel between the distribution of amyloid deposits and neuronal changes, suggesting that the physical influence of the deposited amyloid fibrils was harmful to the nerve rather than the soluble variant TTR itself.

Autonomic disturbances

In the four patients presented here, autonomic dysfunction occurred at an early stage and posed a more serious problem for management than the sensory neuropathy, since it was intractable and restricted ambulation. Falcão de Freitas *et al.* (1980) reported disturbance of the cardiovascular autonomic system in the Portuguese patients with type I FAP including postural hypotension, a low plasma level of noradrenaline both in the supine and standing position, and a blunt response of the heart rate to atropine and Valsalva manoeuvre. All or most of these abnormalities also existed in our patients. The result of the Valsalva manoeuvre indicated impairment of the vagal efferent pathway. The negligible effect of atropine reinforced this conclusion. Administration of noradrenaline led to excessive increases in the heart rate and blood pressure, suggesting denervation hypersensitivity of the α-adrenergic nervous system caused by presynaptic nerve degeneration. However, one must be cautious in interpretation of the responsiveness of the heart rate to various stimuli in the presence of cardiomyopathy. Chronic digestive symptoms such as nausea, diarrhoea and constipation might have been caused by massive amyloid deposition in the intestinal tract as detected by the histopathologic examination.

Central nervous system

There were no clinical signs suggestive of central nervous system (CNS) involvement and no amyloid deposits were found in the autopsied brains. Some Japanese patients with $\mathrm{TTR}^{\mathrm{Met30}}$-related FAP showed cerebellar ataxia and pyramidal tract signs (Ikeda *et al.*, 1987), but these patients apparently had two independent diseases, type I FAP and a spinocerebellar degeneration (Ikeda *et al.*, 1991).

Cardiac involvement

Cardiac involvement was a cardinal feature of our kindred and responsible for sudden death. Cardiac amyloidosis is classified into two types (Coelho and Pimental, 1961); disturbance of rhythm/conduction and congestive heart failure. Our patients showed no clinical sign of heart failure in the early or middle stage, but low voltage and myocardial ischaemic patterns strongly suggestive of cardiac amyloidosis were recorded with the electrocardiogram. Conduction and rhythm abnormalities were mild. In the advanced stage, echocardiogram showed abnormal thickening of both left and right ventricular walls and amyloid cardiomyopathy was confirmed at autopsy in three cases.

Renal involvement

The intensity of amyloid deposition and renal insufficiency may differ considerably even among patients with the mutant gene encoding TTR^{Met30} (Andrade, 1952; Silvia Horta *et al.*, 1964; Andersson *et al.*, 1970, 1976; Hofer and Anderson, 1975; Benson and Cohen, 1977; Ikeda *et al.*, 1987). Our deceased patients (Cases IV-2, V-2, V-6) had well preserved renal function and one patient (Case V-9) has not shown signs of nephropathy. There were only small amounts of amyloid deposits in the perivascular area and rarely in the cortex and medulla at autopsy.

Low serum TTR and elevated CSF protein levels

Serum TTR levels were reduced in our patients. Low TTR levels were also present in Japanese type I FAP (Shoji and Nakagawa, 1988), Portuguese type I FAP and Indian Maryland FAP (Benson and Dwulet, 1983). Although the mechanisms for the reduction of serum TTR is not certain, TTR synthesis was unlikely to be reduced since the TTR mRNA level in livers of patients with FAP was not appreciably different from controls (Mita *et al.*, 1986).

A major proportion of TTR in the CSF is produced in the choroid plexus. The release of TTR from the choroid plexus was enhanced in the Japanese patients with type I FAP (Mita *et al.*, 1986). However, the level of the B-CSF barrier independent TTR in CSF gradually declined in our patient (Case V-6) over 2 yrs. The latter may be explained by consumption of TTR in the intrathecal space as amyloid fibrils, or by compensatory enhancement of TTR synthesis in the choroid plexus at an early stage.

The kindred presented here originated in the Kunimi, Nagasaki Prefecture, but no focus has been located there. This mutation may occur less frequently than the TTR^{Met30} mutation or it might have occurred in the relatively recent past. The patients presented here, though genetically different, were not clinically distinct from the patients with TTR^{Met30}-related type I FAP because of the considerable clinical heterogeneity of the latter reported from many countries. Further studies of a large series of patients over a long period are necessary to ascertain the relationship between the gene mutation and clinical phenotypic expression.

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MOTOR NERVE INEXCITABILITY IN GUILLAIN-BARRÉ SYNDROME

THE SPECTRUM OF DISTAL CONDUCTION BLOCK AND AXONAL DEGENERATION

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SUMMARY

We studied 34 patients with the Guillain-Barré syndrome (GBS) to clarify the clinical significance of inexcitable motor nerves and of low amplitude compound muscle action potentials (CMAPs). The patients were subdivided into two groups Group 1 included eight patients who had electrically inexcitable motor nerves within 2 wks of the first symptom. (Two patients without extensive conduction studies had only one inexcitable motor nerve.) The outcome in this group at 1 yr varied from complete recovery (five patients) to severe motor sequelae (three patients). Group 2 included 26 patients who had two electrophysiological assessments, and in whom the serial changes in CMAP amplitudes were analysed and correlated to outcome. Fourteen of these 26 sets of serial studies were performed within 1 mth. Twelve of 26 patients in Group 2 showed decrease in the amplitude of CMAPs between serial studies; only six of these had a good outcome at 1 yr. Nine of 26 patients showed increase in CMAP amplitude between serial studies, of these eight had a good clinical outcome.

Low-amplitude CMAPs or inexcitable motor nerves in the initial stages of GBS are due to distal pathology of the motor axons, either distal conduction block or axonal degeneration. The nature of these changes cannot be predicted by the results of the initial electrophysiological evaluation, including the presence or absence of active denervation. However, improvement of CMAP amplitude on sequential studies suggests a good outcome at 1 yr. We believe that, in the absence of a biological marker for GBS, individualization of an 'axonal variant' of the syndrome is not warranted at the present time.

INTRODUCTION

In 1986, Feasby *et al.* reported five patients with an acute generalized neuropathy consistent with Guillain-Barré syndrome (GBS), and with inexcitable motor nerves on electrical stimulation. One patient died during the first month of illness, and autopsy studies failed to reveal evidence of inflammation or demyelination in the peripheral nervous system. On this basis, Feasby *et al.* suggested that those cases were an axonal variant distinct from the common primary demyelinating form of GBS. In 1987, Miller *et al.* described four patients with acute onset of widespread paralysis and suggested that they had severe, distal nerve segment pathology. Both groups emphasized the poor prognosis in patients with inexcitability of motor nerves early in the course of GBS.

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Larger series studies in GBS have revealed that the electrophysiological parameter that best correlated to poor outcome is low amplitude of compound muscle action potentials (CMAPs) (Cornblath *et al.*, 1988; Miller *et al.*, 1988). Earlier studies also had suggested that active denervation indicates poor prognosis (Eisen and Humphrey, 1974; McLeod *et al.*, 1976).

We performed this retrospective study to answer the following questions: (i) What is the clinical significance of inexcitable motor nerves early in the course of Guillain-Barré polyneuritis, and does this finding justify the definition of an axonal variant? (ii) What is the relative frequency of distal conduction block in GBS? (iii) Does evidence of distal demyelination indicate a poorer prognosis?

We report here clinical and electrophysiological observations in 34 patients with GBS, eight of whom had inexcitable motor nerves within 2 wks of the first symptom.

PATIENTS AND METHODS

Group 1: patient selection

Eight patients with inexcitable motor nerves were retrieved from the files of the neurophysiology laboratory of the Massachusetts General Hospital (1980–1990: four patients), of Temple University Hospital, Philadelphia and of the University of Texas Health Science Center, Houston (1988–1990: two patients each). All patients met the clinical criteria for GBS defined by Asbury and Cornblath (1990), had electrophysiological testing during the first 2 wks of illness and were followed for at least 1 yr.

Group 2: inclusion criteria

In 26 patients with acquired demyelinating neuropathy who had two or more electrophysiological assessments at the Massachusetts General Hospital, we analysed the serial changes in amplitude of compound motor responses and correlated them with clinical changes between the two studies, and with clinical outcome at 1 yr There were 24 patients with GBS according to the suggested criteria of Asbury and Cornblath (1990). In two patients (Cases 25, 26), initial clinical progression was slightly more protracted than the maximum of 21 d suggested by these authors. Weakness in these patients peaked at 30 d and 35 d, respectively. The first electrophysiological study was performed within 2 wks of onset in 20 cases, within the third or fourth week in four cases, and at day 33 and 37 in two patients.

Electrophysiological studies

Nerve conduction studies were performed using standard techniques, including percutaneous supramaximal stimulation and surface electrode recording. A nerve was considered inexcitable when no response could be evoked by stimulation of the most distal common stimulation site. Amplitudes were measured from baseline to negative peak. In individual nerves, the following changes in CMAP amplitudes were considered significant: (i) a change exceeding ±50% of the previous amplitude if the CMAP amplitude was normal in the first study; (ii) a change of at least ±1 mV between studies if the CMAP was of low amplitude in the first study; (iii) inexcitability of a motor nerve in the second electrophysiological study, regardless of previous CMAP amplitude. In each patient, changes from study to study were considered significant when at least half of the nerves exhibited the same type of amplitude change (relative increase, relative decrease or no significant change). Needle electromyography was performed with standard concentric needle electrodes, and active denervation was sought along four different penetration tracks within each muscle examined.

Clinical status and outcome

Clinical status was graded according to a modified Hughes scale as follows: 0 = healthy; 1 = minor signs or symptoms; 2 = able to walk 5 metres without support; 3 = able to walk 5 metres with support; 4 = bedbound or chairbound; 5 = artificially ventilated; 6 = dead (Hughes *et al.*, 1978). Clinical changes between studies were assessed based on changes in clinical grade. Particular attention was given to the development of muscle wasting in intrinsic hand muscles and anterolateral distal leg muscles during patient examinations. The overall outcome was assessed at 1 yr and graded as good (recovery with minimal sequelae), fair (significant sequelae precluding return to work or independence in activities of daily living) or poor (no recovery or major sequelae; patient chairbound or bedbound).

RESULTS

Clinical data in Group 1 (patients with inexcitable motor nerves) (patients 1–8)

The clinical features of eight patients with inexcitable motor nerves are presented in Table 1 and detailed in the Appendix. All patients were men. Weakness peaked within the first week after onset of weakness in all cases. One patient (patients 1) had dysautonomia and external ophthalmoplegia. Five of eight patients were quadriplegic (three with oropharyngeal weakness), and three patients required ventilatory assistance (two for many months). Three (patients 1–3) had a poor outcome at 1 yr characterized by inability to walk with severe, symmetric distal weakness and marked wasting of lower leg and intrinsic hand muscles. Some muscle power was recovered in proximal muscle groups. Five patients (patients 4–8) had a good outcome at 1 yr.

Electrophysiological studies in Group 1

The electrophysiological data in these eight patients are presented in Table 2. Patients 1–6 showed inexcitability of three or more motor nerves, and patients 7 and 8 showed inexcitability of one motor nerve within 14 d of onset of weakness. Electromyography initially showed decreased or absent motor unit recruitment in each case. Spontaneous activity was noted in three of these eight patients on the first assessment.

TABLE 1 CLINICAL FEATURES OF GBS PATIENTS WITH EARLY INEXCITABLE MOTOR NERVES

Case no	*Age*	*Sex*	*Antecedent illness*	*Time to maximal weakness*	*CSF protein (mg/dl)*	*Plasmapheresis (250 ml/kg)*	*Duration of mechanical ventilation*	*Clinical outcome*
1	76	M	Gastroenteritis (5 d prior)	36 h Arm, leg and bulbar paralysis	136, day 9	Begun day 2, exchanged ×2	+20 mths	Bedbound at 20 mths, ventilator dependent, marked distal atrophy
2	8	M	Appendicectomy (10 d prior)	24 h No movement of arms or legs	120, day 14	None	None	Wheelchair for 24 mths proximal arm movement, no movement of legs, marked distal atrophy
3	58	M	Gastroenteritis (4 d prior)	48 h No movement of arms or legs	35, day 1, 19, day 28	Begun day 5	8 mths	Bedbound at 8 mths, walking at 18 mths, marked distal atrophy and distal weakness
4	5	M	Congenital AIDS, gastroenteritis, candidiasis, URI, weight loss	3 d No movement of arms or legs	39, day 5, 238, day 55	Begun day 7, later received prednisone and gamma globulin	None	*P carinii* pneumonia, walking and using hands at 1 yr, full motor recovery
5	17	M	Infectious mononucleosis (1 wk prior)	5 d Distal limb and bulbar paralysis	40, day 5, 320, day 8	Begun day 7	None	Walking with cane at 2 mths, full recovery
6	13	M	Gastroenteritis (3 wks prior)	4 d No facial or limb movement	59, day 3	Begun day 8	2 mths	Walking with cane at 4 mths, competitive athletics at 1 yr, full recovery
7	34	M	Gastroenteritis (1 wk prior)	7 d No leg movement	60, day 10	Begun day 10	None	Walking with cane at 1 mth, full recovery
8	56	M	URI with myalgias (1 wk prior)	7 d No leg movement	108, day 10	Begun day 14	3 wks	Walking with cane at 2 mths, full recovery

URI = upper respiratory infection

TABLE 2 ELECTROPHYSIOLOGICAL STUDIES IN GBS PATIENTS WITH INEXCITABLE MOTOR NERVES

		Sensory nerves						Motor nerves																					
		Sural		Med		Ulnar		Tibial					Peroneal					Median					Ulnar					EMG	
																												Spon act	
Case		CV	Amp	CV	Amp	CV	Amp	DL	CV	Dist. Amp	Prox Amp	F	DL	CV	Dist Amp	Prox Amp	F	DL	CV	Dist Amp	Prox Amp	F	DL	CV	Dist Amp	Prox Amp	F		
no	Days	m/s	μV	m/s	μV	m/s	μV	ms	m/s	μV	μV	ms	ms	m/s	μV	μV	ms	ms	m/s	μV	μV	ms	ms	m/s	μV	μV	ms	PX	DS
1	2	–	–	45	6	47	8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	0
	18	–	–	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2+	4+
	418	–	–	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1+	3+
2	2	50	20	52	30	48	32	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2·2	52	200	200	NR	0	0
	12	52	10	53	28	50	30	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2·0	53	300	280	NR	1+	0
	20	–	–	50	44	–	–	–	–	–	–	–	–	–	–	–	–	5·3	–	70	NR	NR	–	–	–	–	–	3+	2+
3	3	44	16	46	12	45	10	NR	NR	NR	NR	NR	–	–	–	–	–	7·2	–	210	NR	NR	NR	NR	NR	NR	NR	0	1+
	25	57	10	50	6	53	9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	4+	4+
	240	–	–	46	7	50	4	–	–	–	–	–	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	3+	3+
4	12	–	–	53	23	57	15	NR	NR	NR	NR	NR	–	–	–	–	–	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	4+	4+
	120	–	–	42	9	44	13	5	39	150	40	NR	NR	NR	NR	NR	NR	6	38	150	130	NR	3·6	37	170	130	NR	1+	3+
5	6	NR	NR	–	–	NR	NR	NR	NR	NR	NR	NR	–	–	–	–	–	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	0
6	13	NR	NR	NR	NR	–	–	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1+	2+
7	10	NR	NR	47	12	50	8	–	–	–	–	–	NR	NR	NR	NR	NR	3·8	60	7500	7000	30	2·5	51	2000	2000	33	0	0
8	14	–	–	–	–	–	–	–	–	–	–	–	NR	NR	NR	NR	NR	8·5	26	850	750	NR	–	–	–	–	–	–	–

DL = distal latency, CV = conduction velocity, Amp = amplitude, Dist = distal stimulation, Prox = proximal stimulation F = F wave latency ms = milliseconds μV = microvolts, m/s = metres per second, NR = no response (–) = data not available med = median sensory Spon act = spontaneous activity PX = proximal muscles DS = distal muscles

Clinical disability and distal motor amplitude. Serial studies in 26 patients (patients 9–34)

Twelve of 26 patients showed a decrease in distal CMAP amplitudes when the nerve conduction studies were repeated (Table 3). They included seven patients who had inexcitable motor nerves only in the second electrophysiological assessment. Nine of 12 patients deteriorated clinically between studies, and three did not change. At 1 yr, six of these 12 patients had a poor outcome, and six had a good outcome.

Nine of 26 patients showed improvement of distal CMAP amplitudes (Table 4). Six improved clinically between studies, two did not change and one worsened. Eight patients had a good outcome at 1 yr and one a poor outcome.

Five of 26 patients showed no change in CMAP amplitude between studies. Three had a good, one a fair and one a poor outcome (Table 5).

TABLE 3 GBS PATIENTS WITH SERIAL ELECTROPHYSIOLOGICAL DETERIORATION

Case no	*Age*	*Sex*	*Time to maximal weakness*	*Time to electrophys study*	*Motor nerves*				*EMG Spon act*		*Clinical grade**	*Clinical outcome*
					Tib Amp (μV)	*Per Amp (μV)*	*Med Amp (μV)*	*Uln Amp (μV)*	*PX*	*DS*		
9	65	F	Day 14	Day 7	2000	220	9000	5000	1+	2+	Grade 3	Poor
				Day 30	NR	NR	200	NR	–	–	Grade 5	Grade 6, 3 mths
10	51	F	Day 16	Day 12	–	–	750	320	–	–	Grade 4	Poor
				Day 135	–	–	NR	NR	2+	3+	Grade 5	Grade 4, 12 mths
11	63	F	Day 1	Day 2	90	–	150	100	0	0	Grade 4	Poor
				Day 24	NR	NR	30	NR	1+	2+	Grade 5	Grade 4, 21 mths
12	40	M	Day 1	Day 3	1300	–	–	3400	0	0	Grade 4	Poor
				Day 20	180	NR	–	NR	0	0	Grade 5	Grade 3, 72 mths
13	53	M	Day 10	Day 7	5000	2000	3300	3700	0	0	Grade 3	Good
				Day 20	–	2200	–	1100	0	0	Grade 4	Grade 1, 12 mths
14	74	F	Day 12	Day 12	5000	4200	10 500	10 000	1+	1+	Grade 3	Poor
				Day 95	500	2700	9000	8000	1+	2+	Grade 4	Grade 3, 56 mths
15	44	F	Day 6	Day 5	9200	5400	4500	7700	0	0	Grade 4	Good
				Day 12	1000	34	–	–	–	–	Grade 5	Grade 1, 8 mths
16	34	M	Day 3	Day 2	5500	–	4000	12 000	–	–	Grade 2	Good
				Day 225	1750	200	4800	–	2+	2+	Grade 5	Grade 0, 12 mths
17	57	M	Day 15	Day 7	880	2400	3700	2800	0	0	Grade 3	Good
				Day 45	NR	940	160	1900	0	1+	Grade 4	Grade 1, 12 mths
18	69	M	Day 12	Day 33	480	180	–	–	–	–	Grade 4	Good
				Day 39	NR	NR	–	–	1+	2+	Grade 4	Grade 1, 12 mths
19	46	M	Day 10	Day 5	2700	2160	3300	5200	0	0	Grade 4	Good
				Day 16	1000	1000	2500	1000	–	–	Grade 4	Grade 1, 12 mths
20	52	M	Day 14	Day 6	125	–	5000	–	0	0	Grade 4	Poor
				Day 228	NR	–	7500	–	1+	2+	Grade 4	Grade 6, 13 mths

Tib = tibial, Per = peroneal, Med = median, Uln = ulnar, Amp = amplitude with distal stimulation, μV = microvolts, Spon act = spontaneous activity, PX = proximal muscles, DS = distal muscles, NR = no response, (–) = data not available, * = modified from Hughes *et al* (1978), 0 = healthy, 1 = minor signs or symptoms, 2 = able to walk 5 metres without support, 3 = able to walk 5 metres with support, 4 = bedbound or chairbound, 5 = requires mechanical ventilation, 6 = dead

DISCUSSION

Inexcitability of motor nerve fibres with distal supramaximal stimulation during the first 2 wks of GBS is an unusual electrophysiological finding. It was only present in four of 125 consecutive GBS patients seen in 10 yrs at the Massachusetts General Hospital (3.2%). The incidence of this finding in other series ranges from 1.4% (Albers *et al.*, 1985) to 8.3% (Feasby *et al.*, 1986) of hospitalized patients with GBS. Our eight patients with early inexcitability of motor nerves met established criteria for the diagnosis of GBS (Asbury and Cornblath, 1990). However, the time from first symptom to maximum

TABLE 4 GBS PATIENTS WITH SERIAL ELECTROPHYSIOLOGICAL IMPROVEMENT

					Motor nerves				*EMG* *Spon act*			
Case no	*Age*	*Sex*	*Time to maximal weakness*	*Time to electrophys study*	*Tib Amp (μV)*	*Per Amp (μV)*	*Med Amp (μV)*	*Uln Amp (μV)*	*PX*	*DS*	*Clinical grade**	*Clinical outcome*
21	21	F	Day 5	Day 7	2500	7000	10 500	6500	0	0	Grade 4	Good
				Day 204	15 500	–	–	12 000	0	0	Grade 1	Grade 0, 8 mths
22	35	M	Day 10	Day 12	1500	–	7500	10 000	0	0	Grade 3	Good
				Day 105	15 000	–	15 000	10 000	0	0	Grade 1	Grade 0, 12 mths
23	21	M	Day 17	Day 18	180	–	–	1600	1+	1+	Grade 4	Good
				Day 95	1100	–	–	5000	1+	1+	Grade 3	Grade 1 12 mths
24	16	M	Day 8	Day 16	50	150	–	500	–	–	Grade 5	Good
				Day 908	17 500	3300	–	12 200	–	–	Grade 1	Grade 0, 12 mths
25	76	F	Day 30	Day 10	500	450	2000	200	0	0	Grade 5	Poor
				Day 88	600	2700	6000	4200	–	–	Grade 4	Grade 4, 9 mths
26	36	M	Day 35	Day 28	1200	6300	8000	4000	1+	2+	Grade 3	Good
				Day 56	5000	7800	11 900	8400	–	–	Grade 2	Grade 1, 6 mths
27	77	F	Day 12	Day 14	1400	–	–	3000	0	0	Grade 4	Good
				Day 22	1700	–	–	7500	–	–	Grade 5	Grade 1, 5 mths
28	28	M	Day 20	Day 37	180	–	500	–	0	0	Grade 4	Good
				Day 45	500	–	2300	–	0	0	Grade 4	Grade 1, 12 mths
29	22	M	Day 9	Day 10	–	6500	5000	–	0	0	Grade 3	Good
				Day 17	–	11 000	9000	–	0	0	Grade 3	Grade 1, 12 mths

Tib = tibial, Per = peroneal, Med = median, Uln = ulnar, Amp = amplitude with distal stimulation, μV = microvolts, Spon act = spontaneous activity, PX = proximal muscles, DS = distal muscles, NR = no response, (–) = data not available, * = modified from Hughes *et al* (1978), 0 = healthy, 1 = minor signs or symptoms; 2 = able to walk 5 metres without support, 3 = able to walk 5 metres with support, 4 = bedbound or chairbound, 5 = requires mechanical ventilation, 6 = dead

TABLE 5 GBS PATIENTS WITHOUT SERIAL ELECTROPHYSIOLOGICAL CHANGE

					Motor nerves				*EMG* *Spon act*			
Case no	*Age*	*Sex*	*Time to maximal weakness*	*Time to electrophys study*	*Tib Amp (μV)*	*Per Amp (μV)*	*Med Amp (μV)*	*Uln Amp (μV)*	*PX*	*DS*	*Clinical grade**	*Clinical outcome*
30	69	F	Day 16	Day 9	50	–	700	280	3+	3+	Grade 5	Good
				Day 50	500	–	1300	–	2+	2+	Grade 4	Grade 1, 12 mths
31	21	M	Day 11	Day 12	2600	–	1500	–	0	0	Grade 4	Good
				Day 74	400	–	3200	–	1+	2+	Grade 4	Grade 1, 8 mths
32	31	M	Day 14	Day 10	12 000	–	6000	–	0	0	Grade 4	Good
				Day 17	10 500	–	3600	–	–	–	Grade 4	Grade 1, 12 mths
33	46	M	Day 4	Day 28	700	490	500	120	–	–	Grade 5	Fair
				Day 55	1700	810	1050	120	–	3+	Grade 3	Grade 2, 10 mths
34	65	M	Day 19	Day 14	–	–	4600	5700	1+	2+	Grade 4	Poor
				Day 21	–	–	3500	5300	–	–	Grade 5	Grade 3, 18 mths

Tib = tibial, Per = peroneal, Med = median, Uln = ulnar, Amp = amplitude with distal stimulation, μV = microvolts, Spon act = spontaneous activity, PX = proximal muscles, DS = distal muscles, NR = no response, (–) = data not available, * = modified from Hughes *et al* (1978), 0 = healthy, 1 = minor signs or symptoms, 2 = able to walk 5 metres without support, 3 = able to walk 5 metres with support, 4 = bedbound or chairbound, 5 = requires mechanical ventilation, 6 = dead

weakness was unusually short in all of them. The majority of patients with GBS reached a maximal motor deficit within 2–4 wks after onset of symptoms (Löffel *et al.*, 1977; Arnason, 1984; Ropper and Shahani, 1984), while these eight patients reached maximal deficit within 2–7 d. This very rapid evolution of paralysis is comparable to that reported by Miller *et al.* (1987) (48 h) and by Feasby *et al.* (1986) (5–9 d). However, only three of our eight patients had a poor outcome, with marked residual distal weakness and muscle atrophy 1 yr after onset of illness. Recovery was complete after 1 yr in the remaining five patients, which differs from previous reports of uniformly poor prognosis in patients with early motor nerve inexcitability (Feasby *et al.*, 1986; Miller *et al.*, 1987). The reason for this discrepancy is unclear, but could be the small number of patients in each of these three series. However, the observation that more than half our patients with early inexcitability of motor nerves had fully recovered at 1 yr is important to patient management.

Inexcitability of motor nerves on distal stimulation may be accounted for by either of two pathophysiological mechanisms: degeneration of the motor axons, or conduction block in the terminal segments of the motor axons (Brown and Feasby, 1984). Autopsy studies have shown that the elementary lesion in GBS is focal endoneural lymphocytic infiltration causing focal demyelination with preservation of axonal continuity. This lesion may affect all segments of the peripheral nervous system, including the most distal ones (Alajouanine *et al.*, 1936; Asbury *et al.*, 1969). In some instances, particularly when focal inflammation is severe, axonal degeneration may occur, and is thought to be a secondary phenomenon, or 'bystander' effect (Asbury *et al.*, 1969; Madrid and Wisniewski, 1977). Either demyelination or axonal degeneration secondary to severe inflammation could account for inexcitability of motor nerves, separately or in combination.

The pathological findings reported by Feasby *et al.* (1986) in a single case may be due to the known difficulties associated with autopsy studies of inflammatory neuropathies, which may not detect focal microscopic inflammatory lesions because of incomplete sampling. Additionally, since the patient died on the 28th day of her illness, after developing wasting of distal muscles, it is possible that a fulminant but short-lived inflammatory-demyelinating process was no longer evident (*see below*). The findings of Said (1989) are also possibly biased in favour of an 'axonal variant', since they were biopsy studies of sural nerves. Summation of secondary axonal lesions occurring distal to the dorsal root ganglion may result in severe fibre loss at the level of the distal cutaneous nerve. This is supported clinically by the observations in patient 3 reported by Miller *et al.* (1987), in whom stocking-glove sensory loss affecting all sensory modalities developed within 4 d after symptom onset. Such a pattern of distal sensory disturbances may go unrecognized when it develops in severely paralysed patients.

Our findings indicate that distal demyelinating lesions are not infrequent in GBS, since an increase in CMAP amplitude between serial electrophysiological studies was found in approximately one-third of 26 patients. Additionally, a decrease in CMAP amplitude on consecutive studies may be due to worsening of distal demyelinating lesions, rather than secondary axonal breakdown, as suggested by the observation that half of the 12 patients with this feature in our series made a full recovery at 1 yr. Therefore, we believe that patients with GBS and inexcitable motor nerves represent a heterogeneous group, including some patients with severe distal conduction block (more than 50% in our series), and others with severe, distal inflammatory lesions with marked, early secondary axonal loss. The primary aetiology of this distal lesion, demyelination or axonal degeneration, cannot be confidently predicted by early detection of active denervation in individual patients, since this frequently occurs in GBS patients who recover without sequelae (Ropper *et al.*, 1990). On the other hand, we found that changes in CMAP amplitude on consecutive studies may have prognostic significance. Indeed, serial studies showed an increase in CMAP amplitudes associated with a good prognosis at 1 yr in eight of nine patients in Group 2 (Table 4). Conversely, the finding of delayed inexcitability of motor nerves on serial studies suggests a poor outcome at 1 yr, which was seen in five of six patients with this feature (Table 3).

In our patients with inexcitable motor nerves in the first 2 wks of illness, the first clinical indicator of poor prognosis was the development of distal muscle wasting. This clinical picture is similar to that seen in severe GBS (Ropper, 1986), and is likely due to the development of massive secondary axonal degeneration causing severe motor unit loss. In our material, this clinical pattern was noted both in a subset of patients with early motor nerve inexcitability, and in some patients who developed delayed motor nerve inexcitability. These axonal lesions explain why clinical recovery is both delayed and often incomplete in such patients, since it depends on regeneration and restoration of contact between axonal sprouts and the original targets, rather than on repair of demyelinating lesions in which axonal continuity is preserved.

The clinical variants of GBS and the corresponding electrophysiological findings can be explained by variations in the spatial and temporal patterns of a basic elementary lesion. Three types of clinical variants can be distinguished. Type one: the common form in which the motor deficit is short-lived, and muscle atrophy does not develop; and types 2 and 3 representing the severe variants, characterized clinically by distal muscle wasting developing either shortly after onset (type 2), or rather months after onset (type 3). The type 2 was seen in our patients 1 – 3 with early nerve inexcitability and poor outcome, and in patients reported by Feasby *et al.* (1986) and by Miller *et al.* (1987). The type 3 was seen in patients with inexcitable motor nerves on the second electrophysiological assessment (our patients 9 – 12, 17, 18, 20), who correspond to the 'severe' GBS variant described by Ropper (1986) and by Cros *et al.* (1990). Type 1 corresponds to demyelinating lesions developing in response to a short-lived immunological attack of mild to moderate severity. Although active denervation is often detected by needle electromyography in this variant, the proportion of degenerating axons is small, as corroborated by rapid and complete clinical recovery without sequelae. Type 2, on the other hand, shows rapid development of muscle wasting shortly after onset, due to the fulminant nature of the inflammatory-demyelinating lesions. Suddenness is suggested by the short time interval from symptom onset to peak deficit, and the widespread distribution and severity of the lesions by involvement of the short, distal segments of all motor fibres within a given nerve, causing inexcitability to electrical stimulation. If such severe lesions persist, extensive axonal degeneration occurs, resulting in distal muscle wasting and poor recovery (patients 1 – 3). However, in patients 4 – 8, similarly fulminant inflammatory-demyelinating lesions were presumably so short-lived that massive axonal degeneration did not occur, resulting in good clinical outcome. In type 3, muscle atrophy develops months after onset, suggesting that inflammatory-demyelinating lesions are sustained over a protracted period of time, as indicated by persistent paralysis without atrophy during the first months of illness, caused by conduction block in the motor fibres. Persistent inflammatory changes in peripheral nerves increase the probability of 'bystander' axonal degeneration developing during the course of the illness. The distal predominance of muscle atrophy in these type 3 patients is explained by the summated effects of lesions randomly distributed along the motor fibres (Waxman *et al.*, 1976; Ropper, 1986; Cros *et al.*, 1990).

Clinical elements in support of this hypothesis are as follows. (i) Patients with early inexcitability of motor nerves reach peak disability sooner than patients with more typical GBS, suggesting early widespread lesions. (ii) The majority of our patients with early inexcitability of motor nerves recovered fully within the usual time course of GBS, suggesting that, in these patients, axonal degeneration played little role in early nerve inexcitability. (iii) Patients with early inexcitability of motor nerves and poor outcome develop distal muscle wasting early in the course of their illness, probably indicating massive loss of motor axons due to fulminant onset of inflammatory phenomena. (iv) Patients with secondarily inexcitable nerves may have a clinical course indistinguishable from typical GBS (Cros *et al.*, 1990). This hypothesis is further supported by recent experimental evidence of a dose-dependent relationship between inoculant and the development of secondary axonal degeneration in experimental allergic neuritis (Feasby *et al.*, 1990). A similar relationship was found in passive transfer of experimental allergic neuritis using T cells sensitized to a synthetic myelin peptide (Hahn *et al.*, 1990). Animals in both of these studies displayed a dose-dependent disease spectrum, ranging from mild, slowly progressive symptoms with scattered lymphocytic infiltration and rare demyelination, to severe, rapidly progressive symptoms with prominent cellular infiltration, demyelination and axonal degeneration. We suggest that the immunological attack leading to demyelination in GBS varies in both intensity and duration, and explains an entire spectrum of clinical and electrophysiological findings on the basis of the same primary pathological process.

Finally, the question of the reality of an axonal variant of the GBS remains open. We have shown that the clinical and electrophysiological manifestations of the different presentations of GBS can all be explained by variations in the temporal and spatial distribution of inflammatory-demyelinating lesions. In view of the limited evidence available in support of an axonal form of GBS, we consider the autonomy of such a variant unwarranted at present.

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APPENDIX

Case Reports

Case 1

A 76-yr-old man awoke with diffuse weakness after several days of fever and diarrhoea. Initial evaluation showed MRC grade 2/5 strength in the arms and legs with hypoactive tendon reflexes. The patient rapidly developed respiratory failure; mechanical ventilation was begun in the emergency room. Examination 24 h later showed areflexic flaccid quadriplegia and bulbar paralysis, only the left orbicularis oculi muscle could be contracted voluntarily. Pupillary light responses were preserved The perception of vibration appeared to be impaired distally. Cerebrospinal fluid (CSF) contained 1 wbc and 13 rbcs/mm^3, with glucose 53 mg and protein 29 mg/dl. A repeat CSF examination on day 9 revealed 1 wbc and 72 rbcs/mm^3, with glucose 87 mg and protein 136 mg/dl.

Plasma exchange was begun on day 2. When no improvement was noted after 3 wks, a second course was administered The patient improved minimally during subsequent months, his course was complicated by autonomic instability and nosocomial infections. He regained some bulbar function by 6 mths, but developed severe atrophy of the distal limb muscles.

When re-evaluated at 20 mths, he remained bedbound and dependent on mechanical ventilation. Electrophysiological studies were performed at 2, 18 and 418 d after the onset of the weakness.

Case 2

An 8-yr-old boy developed weakness of the arms and legs while convalescing from an appendicectomy His post-operative course had been complicated by fever and hypotension, weakness appeared over a 24 h period on the patient's 10th postoperative day. Physical examination showed grade 1/5 strength in the arms, and 0/5 strength in the legs Facial diplegia and dysarthria were observed Deep tendon reflexes were absent Sensory examination was normal. Cerebrospinal fluid contained 3 wbcs and 8 rbcs/mm^3, with glucose 68 mg and protein 61 mg/dl A repeat CSF examination 2 wks later showed 1 wbc and 2 rbcs/mm^3, with glucose 77 mg and protein 120 mg/dl

Proximal muscle strength improved during the next 6 wks to grade 2/5 in the arms, and 1/5 in the legs. At 6 mths, strength in proximal muscles was grade 2 – 3/5. He could bear some weight with assistance, however, there was significant atrophy of distal leg muscles. He remains confined to a wheelchair at 20 mths, but has regained functional use of his proximal arm muscles. Electrophysiological studies were performed at 2, 12 and 20 d after the onset of the weakness

Case 3

A previously healthy 58-yr-old man developed ascending paralysis following several hours of leg pain He had recovered from a gastrointestinal illness 4 d earlier Physical examination on his second day of hospitalization showed areflexic quadriplegia with mild vibratory loss Facial and eye movements were unaffected; however, mechanical ventilation became necessary on day 2. Cerebrospinal fluid examined on day 1 contained 2 wbcs and 0 rbc/mm^3, with glucose 70 mg and protein 35 mg/dl A repeat examination on day 28 showed no cells, with glucose 217 mg and protein 19 mg/dl

Plasma exchange was begun on day 5 The patient's hospital course was subsequently complicated by a perforated diverticulum, pneumonia and a pulmonary abscess, no significant improvement was observed during the next 6 mths. By 8 mths after onset of illness the patient was making notable respiratory efforts, although he continued to be mechanically ventilated. Proximal limb-girdle strength and elbow function had improved to grade 2/5. All other limb muscles remained grade 0/5, atrophy of distal musculature was evident By 18 mths the patient was walking with assistance. Distal muscular atrophy and weakness persisted. Electrophysiological studies were performed at 3, 25 and 240 d after the onset of the weakness

Case 4

A 5-yr-old boy with congenital acquired immunodeficiency syndrome (AIDS) was hospitalized with a 1 d history of arm and leg weakness An upper respiratory infection had resolved 1 mth previously He had suffered from fevers, oral candidiasis, diarrhoea and weight loss during the past year. Physical examination on day 1 showed areflexia with grade 1/5 arm strength and grade 2/5 leg strength. Facial and eye movements were unaffected Perception of light touch appeared normal. Weakness continued to progress, and the patient was quadriplegic on day 3. Cerebrospinal fluid examined on day 5 contained 1 wbc and 7 rbcs/mm^3, with glucose 55 mg and protein 39 mg/dl A repeat CSF examination on day 55 of the illness showed 12 wbcs and 0 rbc/mm^3, with protein 238 mg/dl.

Plasma exchange was begun during the first week of illness. When improvement failed to occur, high dose prednisone and gamma globulin were administered during subsequent weeks. Arm movement was first detected 2 mths after onset of weakness. Slow improvement followed, and by 4 mths the patient showed grade 3/5 arm strength. Leg strength was grade 3 – /5 in the proximal musculature and grade 1/5 distally Improvement was complicated by the development of *Pneumocystis carinii* pneumonia; however, full motor recovery was evident at 1 yr Electrophysiological studies were performed at 11 and 120 d after the onset of the weakness

Case 5

A 17-yr-old male high school student was hospitalized with weakness of his arms and legs after 3 d of acroparaesthesiae. Pharyngitis and lymphadenopathy had developed 1 wk previously; numerous atypical lymphocytes and a positive heterophil antibody suggested infectious mononucleosis. Weakness progressed during the first week of hospitalization. Physical examination showed ptosis and facial diplegia. Arm strength was grade 3 + /5 proximally and grade 0/5 distally Leg strength was grade 2/5 proximally and grade 0/5 distally. Deep tendon reflexes were absent Distal sensory loss was evident Cerebrospinal fluid exmained on day 5 of weakness was acellular, with protein 40 mg/dl. A repeat CSF examination on day 8 of weakness also showed no cells, with protein 320 mg/dl.

Plasma exchange was started on day 7 of weakness. Significant improvement in facial and arm strength occurred during the next 2 wks. The patient was subsequently transferred to a rehabilitation facility where improvement continued. When discharged home at 70 d after onset of weakness, he was ambulating with a cane. Distal weakness of the arms and legs resolved over the next 6 mths. Electrophysiological studies were performed 6 d after the onset of the weakness.

Case 6

A 13-yr-old boy was hospitalized with arm and leg weakness Acroparaesthesiae were present prior to hospitalization. A gastrointestinal illness had resolved 3 wks previously Weakness ascended rapidly following hospitalization; mechanical ventilation was necessary on day 2. Physical examination on day 4 showed grade 0/5 limb strength with areflexia and facial diplegia. There was absence of distal sensation Cerebrospinal fluid examined on day 3 of weakness was acellular, with glucose 86 mg and protein 59 mg/dl

Plasma exchange was started on day 8 of weakness. No improvement was noted during the next 3 wks, and the patient's hospital course was complicated by bradycardia, hypertension, gastritis, pneumonia, hypercalcaemia and severe shoulder pain After 1 mth of illness, arm strength had improved to grade 1/5 Improvement continued during the next month, and mechanical ventilation was discontinued. When transferred to a rehabilitation centre 9 wks after the onset of weakness, the patient's strength was grade 3 + /5 in the arms and grade 2/5 in the legs. He could stand briefly with support. The patient was walking with a cane 4 mths after the onset of his illness. Recovery continued, and he returned to competitive athletics within 1 yr of his illness. Electrophysiological studies were performed at 13 d after the onset of the weakness.

Case 7

A 34-yr-old dentist noted leg weakness several days after recovering from a gastrointestinal illness. Physical examination 10 d after the onset of neurological symptoms showed tendon areflexia. Strength was grade 4/5 in the arms. Leg strength was grade 3/5 proximally; however, no distal leg movement was observed. Cranial nerve function and sensory testing were both normal. Cerebrospinal fluid examined 10 d after the onset of weakness was acellular with protein 60 mg/dl.

The patient was hospitalized, and plasma exchange was begun. The patient's clinical status remained stable during the next week. Improvement followed, and the patient was walking with assistance when discharged home 2 wks later. He recovered fully during the next 6 mths. Electrophysiological studies were performed 10 d after the onset of the weakness.

Case 8

A 56-yr-old man was hospitalized with progressive leg weakness following several days of back pain and acroparaesthesiae. He had recently recovered from an upper respiratory infection associated with severe myalgia. Weakness ascended rapidly, and mechanical ventilation was necessary. Physical examination 7 d after the onset of weakness showed grade 2/5 arm strength and a mild facial diplegia. Deep tendon reflexes were absent and there was no leg movement. Distal sensory loss was evident Cerebrospinal fluid examined on day 10 of the weakness was acellular, with protein 108 mg/dl.

Plasma exchange was started 14 d after the onset of the weakness Improvement followed during the next several weeks. Mechanical ventilation was discontinued 1 mth after the onset of the weakness, and the patient was soon standing with assistance. He was walking with a cane when transferred to a rehabilitation facility 1 mth later, and recovered fully over the next 6 mths. Electrophysiological studies in this case were performed 14 d after the onset of the weakness.

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NEUROLOGY OF LATENT NYSTAGMUS

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SUMMARY

We report eye movement findings in 30 patients with latent nystagmus and who were found to have a variety of associated oculomotor disorders.

Latent nystagmus is defined clinically as nystagmus which appears on covering one eye and beats towards the uncovered eye. Recordings showed that the latent nystagmus in 28 patients had slow phases with linear or exponentially decreasing velocity. This nystagmus is termed 'LN'. In 13 of these patients certain manoeuvres (e.g. pursuit) provoked nystagmus with exponentially increasing slow phase velocities characteristic of the congenital form of nystagmus termed 'CN' and we propose that this is a forme fruste of CN. In two patients the nystagmus provoked by cover was latent CN.

Twenty-nine patients had a history of strabismus and one had a marked phoria. Some patients had amblyopia whilst others had normal vision in each eye. Although binocular vision was usually absent, six patients had varying degrees of stereopsis.

A temporonasal predominance of monocularly elicited optokinetic response previously associated with LN, was present only in a minority of patients. Some responses were bidirectionally absent or of low velocity, possibly the result of a cortical impairment of visual motion detection. The most deranged responses had slow phases which were in the opposite direction to the stimulus as described in CN. The presence of 'forme fruste' CN in many of these patients suggests that some of the derangements of optokinetic responses are due to CN. The findings indicate a greater overlap between the incidences of LN and CN than previously estimated.

Thirty percent of patients had large saccadic 'square wave' intrusions. These were not present when there was marked amblyopia. They are attributed to a competitive incongruence of visual fields and eye positions.

Dissociations found between the presence and severity of strabismus, stereopsis, amblyopia and optokinetic abnormalities point to these features being relatively independent although associated in typical clusterings. This is evidence against the theory that strabismus and LN are directly caused by nasotemporal optokinetic imbalance which persists because of failure to develop binocular vision. The variability of findings favours the view that LN and CN arise from a genetic or acquired embryological disorder with various degrees and directions of expression.

INTRODUCTION

The term latent nystagmus is used to refer to a nystagmus which appears or is markedly enhanced when one eye is covered with the uncovered eye free to view. The uncovered eye drifts off target with a slow phase movement in a nasal direction. The drift is corrected with a nystagmus beat in a temporal direction to refix the eyes on target. The eye under cover also moves with the same nystagmus waveform, although sometimes with different amplitude if it is in an extreme orbital position.

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Latent nystagmus is most commonly associated with infantile or childhood onset esotropia and amblyopia. In addition, subjects with latent nystagmus are reported to have a poor monocular optokinetic response to target motion in a nasotemporal direction (Tychsen and Lisberger, 1986; Kommerell, 1988). Nasotemporal asymmetry of optokinetic nystagmus (OKN) is physiological in the neonate (Atkinson and Braddick, 1981; Naegele and Held, 1982) and it has been suggested that its persistence is the fundamental abnormality in infantile esotropia. Some subjects with LN also have 'dissociated vertical deviation' (DVD) which is an elevation and extortion of the eye under cover.

Latent nystagmus waveforms: LN or CN?

A nystagmus that is latent may have two different types of waveform. Although they are both generically 'congenital' the two waveforms imply different kinds of mechanism (Dell'Osso *et al.*, 1979; Dell'Osso, 1985). Accordingly, one must adopt precise criteria to distinguish between these two varieties which necessarily depend on eye movement recordings (Dell'Osso and Daroff, 1975; Dell'Osso *et al.*, 1979). One latent type of nystagmus has a slow phase with exponentially decreasing or linear velocity in all positions of gaze; this is termed 'LN'. A second type has slow phases with exponentially increasing velocity involving a complex variety of waveforms and is termed 'CN'. (The CN type may be more familiar to the reader as the conjugate spontaneous or gaze-evoked nystagmus, often of florid appearance and present with binocular viewing.) Both LN and CN can coexist in a patient with either being the more dominant waveform or mixed in equal proportions; LN and CN with a marked latent component are illustrated in Fig. 1.

The present study examined the relationships between ophthalmological and oculomotor findings in a sample of patients with latent nystagmus with emphasis on optokinetic responses because of their relevance to theories of latent nystagmus and strabismus. The findings also have implications for clinical diagnosis since latent nystagmus can be associated with a number of oculomotor abnormalities resembling disorders in acquired neurological disease. Accordingly, recognition of the characteristics of latent nystagmus may obviate extensive investigations.

METHODS

Patient selection

Thirty patients were admitted to the study because examination in the clinic had revealed a nystagmus which was provoked by cover testing and which beat towards the uncovered eye. Patients who had a clearly visible, persistent, spontaneous or gaze-evoked nystagmus with both eyes viewing were excluded from the study on the basis that such nystagmus was likely to be CN. The selection included patients with very small amplitude 'manifest LN' which was markedly enhanced on cover testing and was sometimes detected on clinical examination. All patients found to have relevant neurological disease were excluded from the study. These criteria were aimed at biasing selection against including patients with obvious features likely to be CN.

Eye movement recordings

Eye movements in the horizontal plane were recorded from separate eyes with DC coupled electro-oculography. Occasionally infrared corneal reflection oculography (bandwidth DC >100 Hz) was used on children who would not tolerate electrodes. Recordings were made of eye movements in primary gaze and 30° right and left gaze with both eyes viewing and with each eye separately occluded.

All but the six youngest subjects (aged 5–7 yrs) underwent vestibular testing of the horizontal vestibular ocular reflex on the motorized chair using rotational velocity steps or sinusoidal oscillation in darkness. Vestibular function will not be discussed because it is known to be normal in LN (Tychsen *et al.*, 1985). However, vestibular responses were useful for classifying patients because they sometimes have waveforms suggestive of CN.

Optokinetic and pursuit stimuli

Pursuit and optokinetic responses were tested on all subjects with both eyes viewing and with each eye separately occluded.

Pursuit stimuli comprised a red laser dot target moving over a plain blue background with a sinusoidal trajectory at frequencies variable from 0.1 Hz to 0.8 Hz with a peak amplitude of 20°.

Optokinetic testing was aimed at determining how responses were related to stimulus velocity and also to position of the eyes in the field of gaze after the methods of Halmagyi *et al.* (1980) and Kommerell and Mehdorn (1982). Optokinetic stimuli were delivered with a 2 m diameter, whole field rotating drum with an illuminated inner surface of black and white vertical stripes, each subtending 10°. The subject was seated in the centre of the drum with head restrained.

The procedure consisted of accelerating the drum at 10 deg/s^2 from rest up to 80 deg/s. The acceleration was interrupted at 20, 40, 60 and 80 deg/s so that the drum rotated at constant velocity at these speeds. During constant velocity stimuli the subject was instructed to look at the portion of the drum which was straight in front and also to look at the drum with his eyes deviated over to the right and to the left by about 25–30°. After the 80 deg/s stimulus the drum decelerated to rest To plot the graphs shown in Fig. 5, slow phase eye movement velocity was measured by aligning a protractor radius with the linear slow phases and measuring the inclination. Averages of the velocities of each slow phase occurring during a 4 s interval taken when the eyes were in the required field of gaze were calculated.

RESULTS

General patient characteristics

Essential clinical features of the patients surveyed are given in Table 1. Twenty-eight patients had a history of strabismus beginning in childhood. When examined, 15 were convergent, eight were divergent and one alternated. Four of the patients with childhood strabismus had straight eyes following surgery or patching. Two patients had no history of strabismus but were noted to have phorias (in phoria the eyes are normally orthotropic but immediately drift into misalignment when covered).

Four patients had gross binocular vision (BV) at 400′ to 800′ arc and one had good stereopsis at 70′ of arc (measured by synoptophore or on Stereo Optical Company Inc., Stereo Test). This latter patient also had CN-type nystagmus in the far right lateral gaze which had been undetected in the initial clinical selection. Unfortunately, BV was not assessed in the two patients without strabismus. However, rapid return to orthotropia on removing cover indicates that they had some useful BV. Thirteen patients had a amblyopic eye in which visual acuity was equal to or less than 6/18. However, 10 had acuities in both eyes equal to or better than 6/9.

Dissociated vertical divergence was present in 12 patients of whom nine had been operated on to correct the strabismus. In all, 13 patients had received surgery on the extra-ocular muscles. Two had botulinum toxin injections.

Patients 4 and 5 were sisters and patients 28 and 29 were mother and daughter. A further five patients had a family history of strabismus.

Symptoms. Although not commonly appreciated, latent nystagmus may be symptomatic.

TABLE 1 PATIENT CLASSIFICATION

Patient no /sex and age (yrs)	*Acuities diagnosis*	*Original diagnosis*	*Present diagnosis*	*Treatment*	*Other history*	*CN?*	*BV?*
1 F 9	R6/9 L6/9	RCS	RCS DVD	Surgery ×2		+	–
2 M 6	R6/12 L6/18	LCS	RCS	Glasses		+	–
3 M 27	R6/18 L6/9	?	RDS DVD		Paroxysmal head shaking somatic tics, epilepsy	+++	–
4 F 13	R6/18 L6/24 BEO 6/5	ACS	LCS L/R DVD	R patch	Mild cerebellar syndrome? Patients 4 and 5 are sisters	+	–
5 F 11	R6/6 L6/24+ BEO 6/5	LCS	LCS	R patch Surgery ×2 Glasses		?	–
6 M 33	R6/6 L6/6	Childhood 'squint'	R. exophoria	Patching	Anxiety complex	+++++	–
7 M 7	R6/36 L6/5	RCS	RCS accommodative	Surgery ×1 Glasses	Speech therapy Opsoclonus?	+	–
8 M 44	R6/5 L6/5	?No strabismus—marked esophoria			L ptosis	++++	?
9 M 13	R6/18 L6/4	RCS	RDS	Surgery ×1 Patching, glasses	'Clumsy child'	?	–
10 F 21	R6/12 L6/18 BEO 6/6	?	LDS (minimal)			CN	–
11 F 15	R6/9 L6/9 pt BEO 6/9	LCS DVD	LCS DVD	Glasses		?	400'
12 M 16	R6/12 pt L6/9 BEO 6/5	ACS	LDS DVD	Surgery ×4	Hyperactive, learning problems	+	–
13 M 10	R6/9 L6/18	LCS	LCS DVD	Surgery ×1 Glasses	*	?	–
14 M 5	R6/12 L6/6	RCS	RCS DVD	Surgery			–
15 M 38	R6/6 L6/6	RDS	RDS			++++	–
16 M 38	R6/6 L6/6	?	ADS			?	–

17 F 6	R6/9 L6/12 BEO 6/6	ACS	LCS DVD	Surgery Glasses			–
18 F 6	R6/9 L6/12 BEO 6/6	ACS nystagmus head nodding	LCS DVD	Surgery Glasses			–
19 F 41	R6/6 L6/6	CS	RCS DVD	Surgery	**		–
20 F 10	R6/6 L6/36	ACS	LCS DVD	Surgery Glasses	*****		–
21 M 25	R6/9 L6/24	?	LCS				–
22 F 6	R6/12 L6/9		RC-DS		Albinism***		400′
23 M 67	R3/60 L6/24 BEO 6/9		RDS				400′/800′
24 M 19	R6/6 L6/6		ADS	Botox			–
25 F 20	R6/6 L6/6	?Exotropia	Straight	R patch	(Enhanced by accident)	CN	70′
26 F 35	R6/9 L6/18		LCS				–
27 F 24	R6/6 L6/5	No history of strabismus, eyes straight with mild phoria			(Enhanced by accident)	+++	?
28 F 42	R6/6 L6/6	CS	Looks straight	Surgery ×2	Patients 28 and 29 are mother and daughter****		–
29 F 11	R6/6 L6/6	CS	Looks straight DVD	Surgery ×2			–
30 M 42	R6/9 L6/12		L/ACS		Enhanced spontaneously		400′

*Sister with strabismus without LN, **daughter with strabismus without LN, ***brother with strabismus and albinism without LN, ****second daughter with strabismus without LN, *****mother and sister with strabismus without LN Binocular vision assessed on Titmus fly test and synoptophore 'Botox' signifies that patients had received botulinum toxin for correction of strabismus The presence of CN in patients' eye recordings was quantified in rank order by awarding a + for each manoeuvre which provoked a CN waveform The manoeuvres included were: cover testing of right and left eye, gaze holding to the right and left, pursuit under monocular and binocular conditions, optokinetic responses in primary and to right and left gaze and monocular and binocular responses considered as separate conditions and vestibular evoked nystagmus Possible CN waveforms were ascribed a ? Binocular vision is rated in minutes or arc or – indicates no BV RCS = right convergent strabismus, LCS = left convergent strabismus; RDS = right divergent strabismus, LDS = left divergent strabismus, ACS = alternating convergent strabismus, ADS = alternating divergent strabismus, RC-DS = right convergent-divergent strabismus, DVD = dissociated vertical deviation

Four patients were significantly disabled, either with monocular viewing or when the nystagmus became manifest, and had acuities of 6/12 or worse. Amongst these was the highest velocity of pure LN (without CN) recorded at 25 deg/s immediately following cover which settled down to 21 deg/s (patient 23). A further patient had his career as a soldier thwarted because his LN impaired his ability to sight a gun. Three patients were disturbed by oscillopsia because the amplitude of their nystagmus had increased in later life, one spontaneously (pure LN) and the others following accidents involving minor head trauma (CN with marked latent component).

Characteristics of latent nystagmus

The nystagmus provoked on cover testing took two different waveforms as illustrated in Fig. 1. In 28 patients the slow phases of the nystagmus had linear or decreasing velocities. The nystagmus was invariably unidirectional beating to the uncovered eye, sometimes tended to decay in amplitude and occasionally would cease entirely. One would tend to classify this nystagmus as LN (Dell'Osso *et al.*, 1979). However, careful scrutiny of the eye movement recordings revealed that half of these patients had occassional nystagmus with CN waveforms (documented below). These patients are tentatively classified as predominately LN with a CN component. In two subjects the LN had slow phases which had increasing velocities characteristic of CN-type nystagmus; this we will refer to as 'latent CN'. One of these was initially evoked beating to the

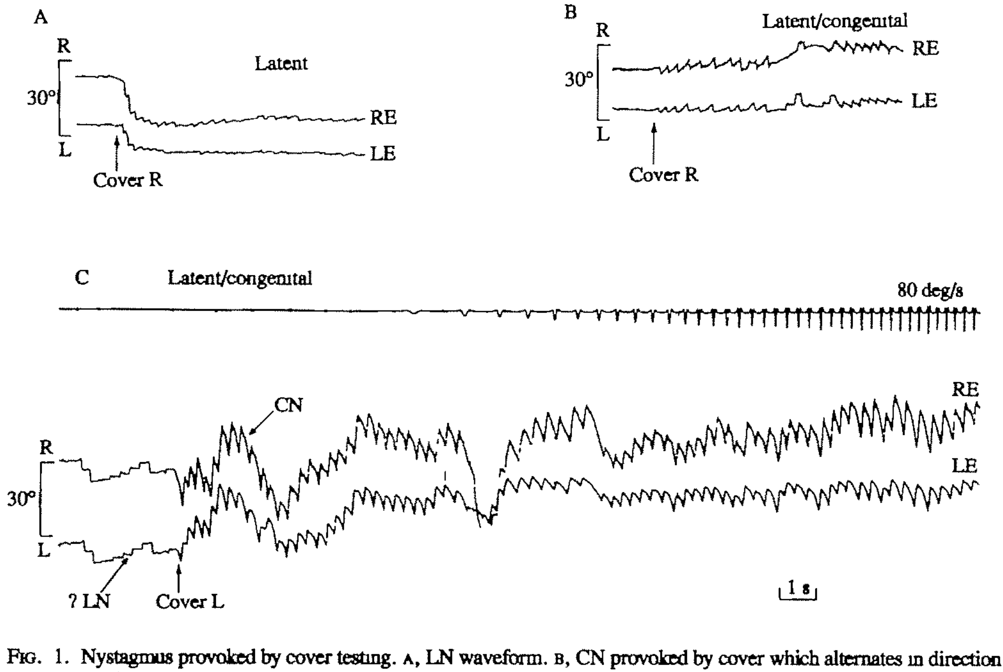


FIG. 1. Nystagmus provoked by cover testing. A, LN waveform. B, CN provoked by cover which alternates in direction. C, before covering there is an exponentially decreasing velocity nystagmus suggestive of manifest LN. However, covering provokes CN which is apparently unaffected by the optokinetic stimulus Note: in A the changes in eye positions on covering as the dystropic eye assumes fixation; convergence of the eyes under cover in A and C; divergence of the eyes in B. The tracings are for patient 5 (A), patient 1 (B) and patient 8 (C). RE = right eye; LE = left eye.

uncovered eye but subsequently cyclically reversed direction and altered waveform typical of alternating CN.

In most patients, on careful scrutiny, nystagmus of variable amplitude and persistence could be detected when both eyes were uncovered (Fig. 1c). One patient (6) had latent nystagmus only when he was fixating near targets when his phoria would break down into strabismus. This underlines the importance of testing with both near and far targets.

Horizontal optokinetic responses in latent nystagmus

Interpretation of optokinetic responses in the presence of an ongoing nystagmus is hazardous because the response interacts with the nystagmus, the nystagmus causes its own uncontrolled retinal stimulus and visual motion signals to the oculomotor system interact with the mechanisms of the nystagmic instability. Varying the stimulus from low to high velocity, ranging above and below the ongoing nystagmus slow phase velocity, ensures that an adequate retinal slip stimulus is delivered, at least at some velocities. Even with complex nystagmus waveforms this technique shows whether there is sensitivity to an optokinetic stimulus by velocity-dependent changes in nystagmus waveform or direction. The results showed great variability. In some patients optokinetic responses appeared fully normal or of normal symmetry but low velocity. Other patients had marked derangements as described below.

In many subjects the direction of the slow phase of the nystagmus recorded during an optokinetic stimulus could vary independently of stimulus direction or with the position of the eyes in the field of gaze. Examples are given. Figure 1: a CN with a marked latent component which does not change in appearance by the introduction of an optokinetic stimulus. Figure 2: cyclic reversals of the direction of nystagmus during binocular viewing of a unidirectional stimulus. The reversals occur with the eyes in either right or left gaze. Figure 3: inversion of nystagmus direction at higher stimulus velocities during monocular viewing with the eyes approximately in the same position of gaze; of note, both of these records were taken from a subject without evidence of CN in the waveform of his nystagmus. Figure 4: the direction of nystagmus during a constant velocity stimulus changes with gaze. When the nystagmus slow phase direction

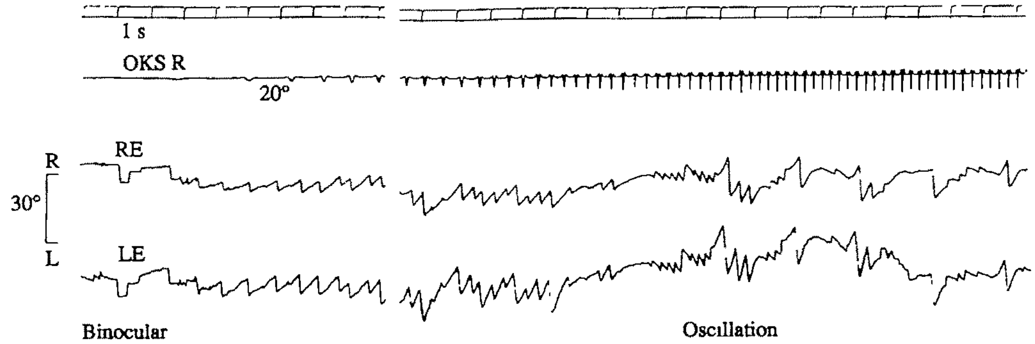


FIG 2. Responses to optokinetic stimuli (OKS) showing normal appearance at low stimulus velocities with cyclic reversals of the direction of the nystagmus 'inverted OKN' at higher stimulus velocities. The blips on the optokinetic stimulus trace are 20° intervals crossing primary gaze. Patient 13 who had no evident CN RE = right eye, LE = left eye

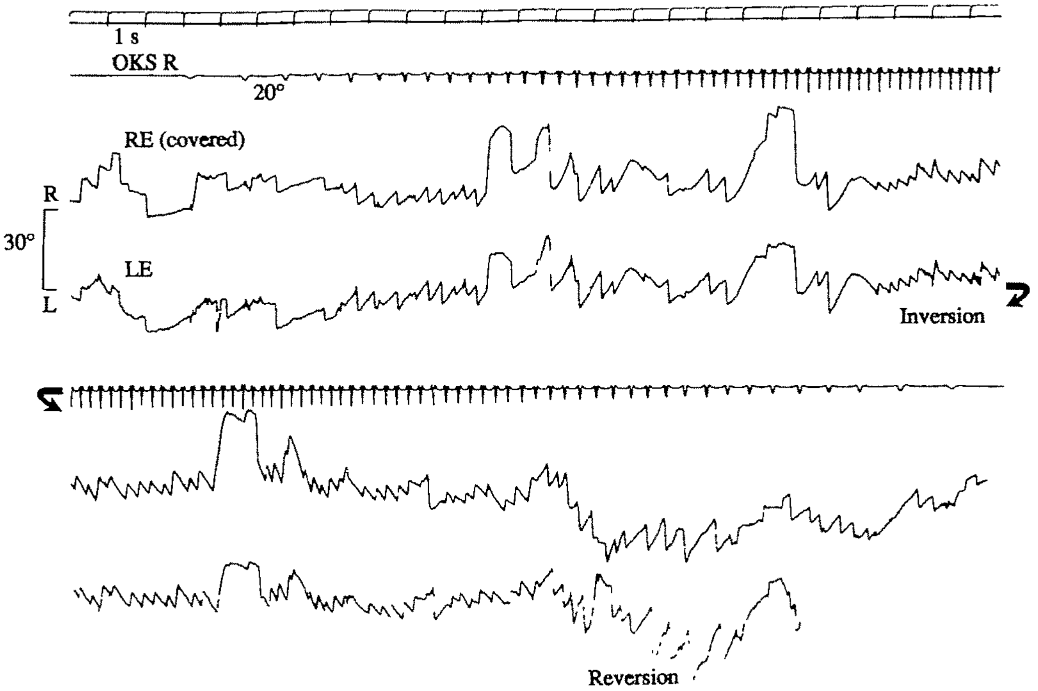


FIG 3. Responses to optokinetic stimuli (OKS) showing inversion of the direction of the nystagmus at higher stimulus velocities and reversion to nystagmus in the appropriate direction with decreasing stimulus velocity. Patient 13 who had no evident CN RE = right eye; LE = left eye

is opposite in direction to the stimulus the waveform is CN. The gaze dependency may be determined by position of the null point in the CN.

Graphical analysis of examples of optokinetic responses showing the variety of response patterns are given in Fig. 5A,B,C,D.

Figure 5A shows near normal responses with a slight directional preponderance of leftwards slow phase during binocular and right eye viewing and a right directional preponderance with left eye viewing. This temperonasal > nasotemporal asymmetry of OKN, commonly said to be typical in LN, was seen in only four patients of whom one (patient 22) had partially expressed oculocutaneous albinism. The directional asymmetries which can be more than 20 deg/s are not a simple summation of LN with the OKN and an additional explanation must be sought.

Figure 5B shows the responses of subject whose raw data records are given in Fig. 4. With monocular viewing there is a velocity saturation of nystagmus slow phase at about 20–30 deg/s rightwards and leftwards and the direction of the slow phase is inverted with respect to the stimulus direction if the eyes are deviated in the direction of drum rotation. Binocularly there is still velocity saturation which are below normal, to the right at 30 deg/s and to the left at 20 deg/s with reversal of nystagmus direction when the eyes are deviated to the left.

Figure 5C shows responses whose velocities with binocular and right eye viewing

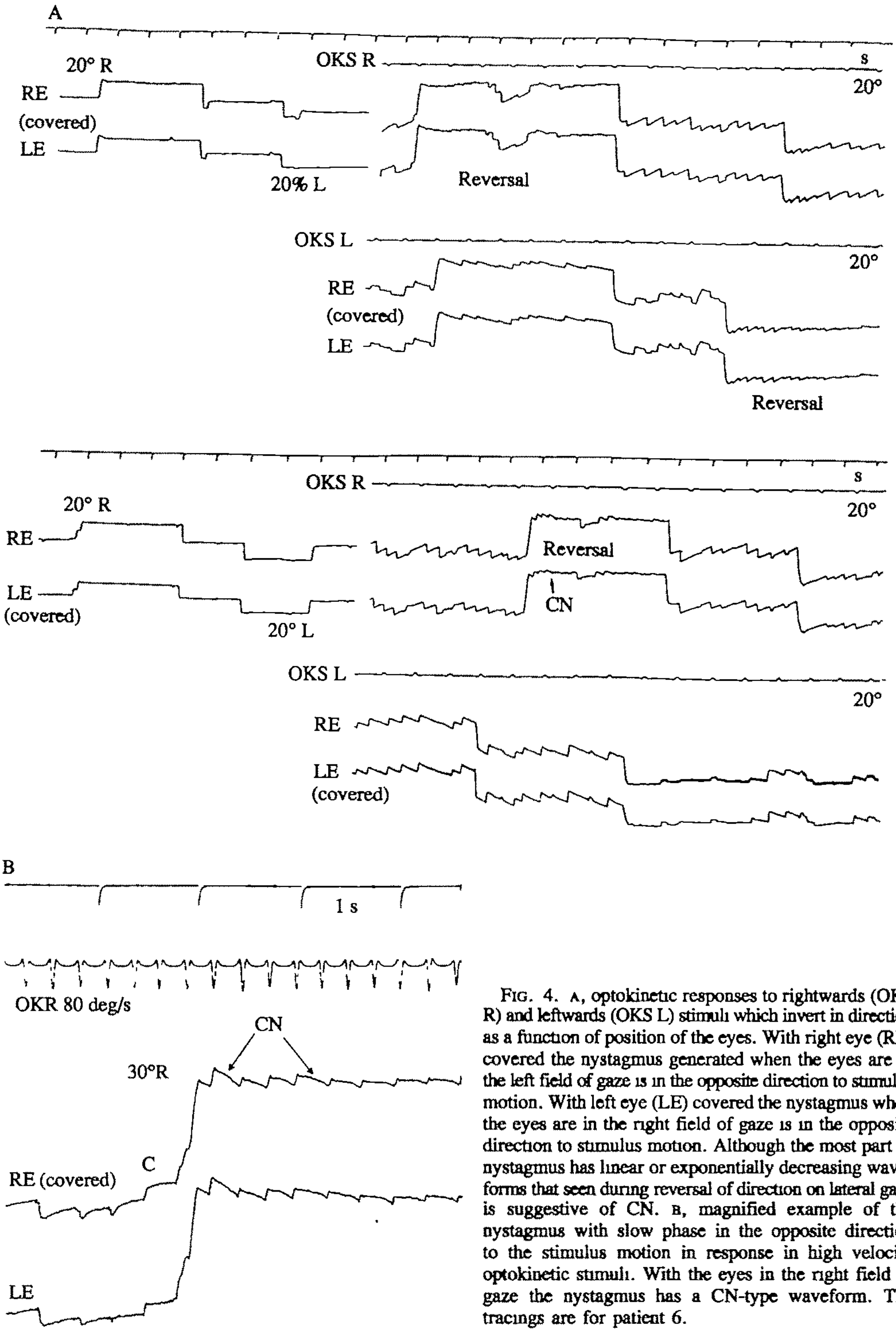
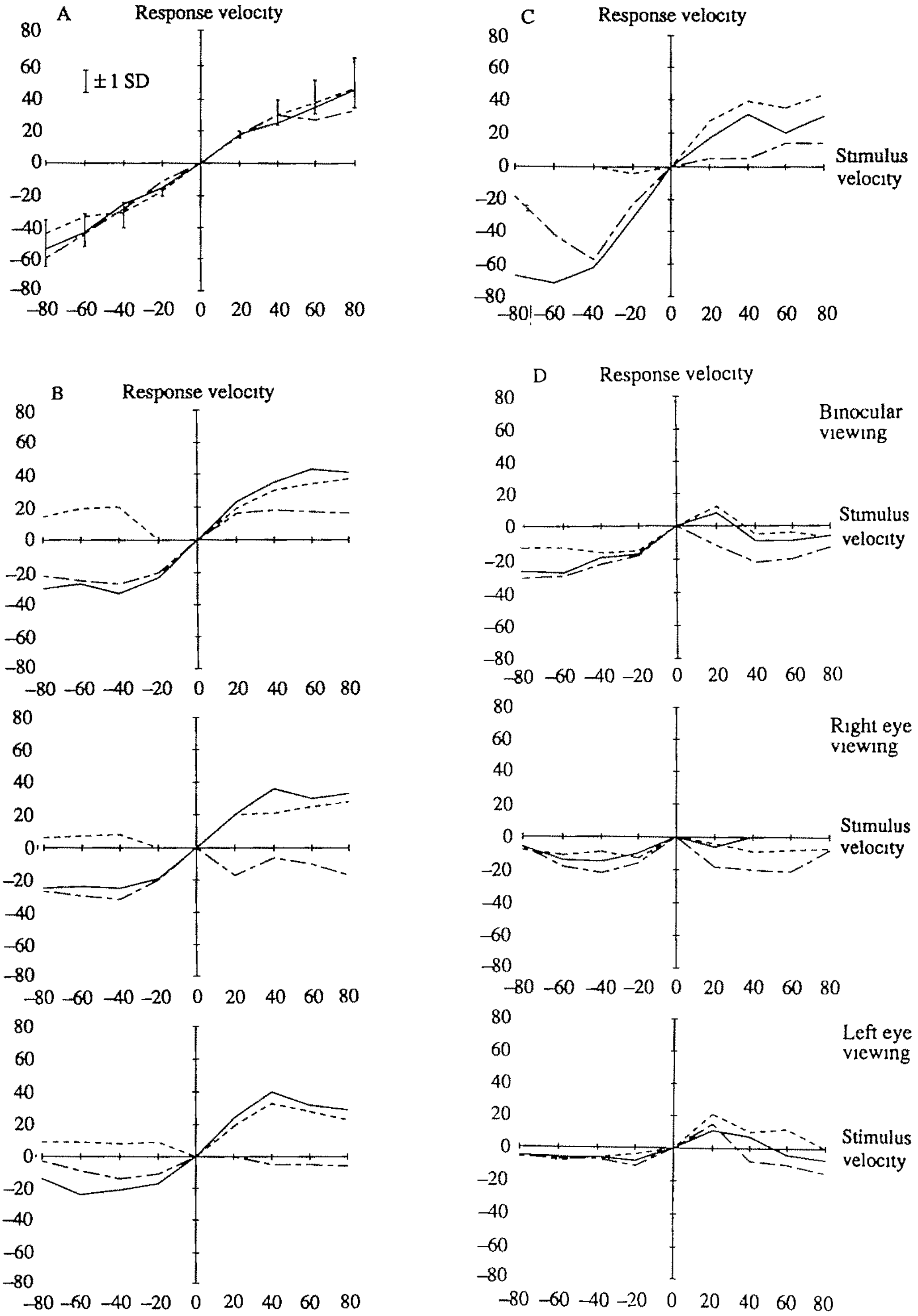


FIG. 4. A, optokinetic responses to rightwards (OKS R) and leftwards (OKS L) stimuli which invert in direction as a function of position of the eyes. With right eye (RE) covered the nystagmus generated when the eyes are in the left field of gaze is in the opposite direction to stimulus motion. With left eye (LE) covered the nystagmus when the eyes are in the right field of gaze is in the opposite direction to stimulus motion. Although the most part of nystagmus has linear or exponentially decreasing waveforms that seen during reversal of direction on lateral gaze is suggestive of CN. B, magnified example of the nystagmus with slow phase in the opposite direction to the stimulus motion in response in high velocity optokinetic stimuli. With the eyes in the right field of gaze the nystagmus has a CN-type waveform. The tracings are for patient 6.


A
Response velocity
±1 SD
80
60
40
20
0
−20
−40
−60
−80
−80 −60 −40 −20 0 20 40 60 80
C
Response velocity
Stimulus velocity
B
Response velocity
D
Response velocity
Binocular viewing
Stimulus velocity
Right eye viewing
Stimulus velocity
Left eye viewing
Stimulus velocity

exceeded stimulus velocity for leftwards stimuli up to a saturation at 60 deg/s. Responses for nasalwards stimuli were absent on monocular viewing.

Figure 5D shows responses to optokinetic stimuli which consist of a persistent right beating nystagmus with low slow phase velocities under almost all testing conditions. This subject had a marked right beating LN with no evidence of CN so one might have thought that any leftwards optokinetic response would be enhanced with the nystagmus. This was not the case which raised doubt as to whether there is any response in this direction. The uniformity of the nystagmus during optokinetic stimuli suggests that it might be an instability, triggered off in some way by the stimulus.

Vertical optokinetic in latent nystagmus

On clinical examination using a hand-held target or drum, most patients had apparently normal or near normal vertical optokinetic and pursuit responses both with monocular and binocular viewing, despite marked horizontal abnormalities. This finding demonstrates the independence of the horizontal and vertical systems. Several patients had sluggish responses, particularly during monocular stimulation, but in the absence of quantification their significance is uncertain. These sluggish responses were not systematically associated with DVD as one might expect. Of note, vertical optokinetic responses could appear normal with monocular stimuli presented to a severely amblyopic (6/18−36) eye.

Pursuit responses

Pursuit response abnormalities were similar to OKN abnormalities and there was no evidence of dissociation between optokinetic and pursuit performance in the form of robust pursuit and deranged OKN. In some patients optokinetic responses were better formed than pursuit, probably because the larger target is a stronger stimulus. Of note, pursuit was particularly provocative of saccadic square wave intrusions (Fig. 6).

Presence of 'forme fruste' of CN-type nystagmus

Fifteen patients whose LN had linear or exponentially decreasing waveforms were found to have CN-type nystagmus waveforms during certain manoeuvres, in particular during pursuit and optokinetic stimulation. For example, in Fig. 4, when the eyes are in the right field of gaze, the nystagmus slow phase is in the opposite direction to the motion of the optokinetic drum and has a complex waveform similar to CN. This waveform is not the result of an interaction between gaze-evoked nystagmus and an optokinetic response since it does not occur in all circumstances when the two are opposed in direction but is specific to certain eye positions. In the context of clinical diagnosis a spontaneous nystagmus with this waveform would normally be taken as evidence for CN (Gresty *et al.*, 1984; Kelly *et al.*, 1989) and therefore we propose that this is a 'forme fruste' of CN. The extent to which CN waveforms were evident in a subjects

FIG. 5A,B,C,D. Plots of slow phase eye velocity as a function of stimulus velocity for various subjects with the eyes in centre, right and left gaze and with binocular or monocular viewing. The vertical lines on plot A are the ±1 SD limits of normal performance according to our laboratory standards. Rightwards direction is positive. A and C ——, binocular; – – –, right eye; – – –, left eye. B and D: ——, look centre, – – –, look right; – – –, look left Tracings are for patient 28 (A), patient 6 (B), patient 9 (C) and patient 23 (D)

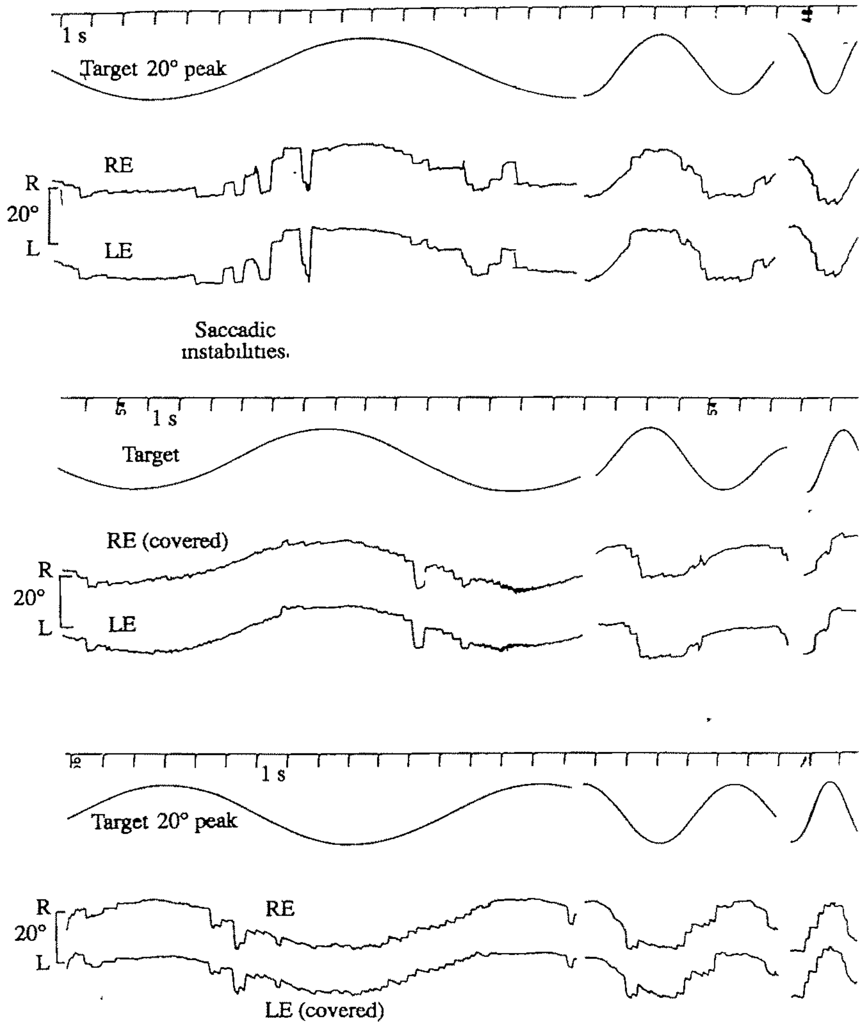


FIG 6. Pursuit responses to a sinusoidal target (patient 9) Square-wave saccadic intrusions can be during either leftwards or rightwards pursuit with monocular or binocular viewing, consistently taking the eyes towards the left. Note slow phases opposite to target motion with left eye (LE) following leftwards and the right eye (RE) following rightwards.

eye movements is shown in the tables for direct comparison with the incidence of other features. Ten patients had CN which was provoked consistently by certain manoeuvres and a further five had occasional brief episodes of CN.

Saccade abnormalities: saccadic square-wave intrusions

Eleven patients had involuntary saccades or series of saccades which took the eyes away from the location of the target which the subject was required to fixate or pursue and then returned the eyes back on target giving an overall shape of 'square-wave intrusions' (Fig. 6). If subjects failed to suppress these movements after encouragement and practice to stay 'on target' and episodes occurred frequently, their saccadic control was judged to be abnormal. The amplitudes of the square waves could be as high as 20° and occurred with monocular or binocular viewing. Pursuit was particularly provocative of square-wave intrusions (Fig. 6).

Relationships between LN, CN, amblyopia, OKN and square-wave intrusions

The strength of associations between the various features accompanying LN is relevant to establishing those which always occur together and may be causally related. Since the 'strength' of appearance of certain features was highly variable and difficult to measure as a magnitude, these features were rank ordered according to the criteria given in Table 2

TABLE 2 DERANGEMENT OF OPTOKINETIC RESPONSES IN LN AND RELATIONSHIP WITH CN, AMBLYOPIA AND SACCADIC INSTABILITY

Patient	*Binocular*		*R eye*		*L eye*			*Amblyopia?*	
no./sex and age (yrs)	*R*	*L*	*R*	*L*	*R*	*L*	*CN waveform*	*6/18+*	*Square waves*
21 M 25								+	
28 F 42									
22 F 6			+̲?̲			+̲?̲			R+L
1 F 9*				+			+		R+L
29 F 11						+			L
26 F 35						+		+	
11 F 15	+						??		
27 F 24	+	+					+++		R+L
19 F 41			+̲		+̲?̲	+̲			R
13 M 10		+			+	+	??	+	
14 M 5	+		+	+					
17 F 6			+̲	+̲		+̲			
4 F 13*			+	+	+		+	+	
20 F 10			+	+	+			+	
24 M 19	+				+	+			L
15 M 38	+		+̲		+̲	+̲	++++	+	
5 F 11*			+	+	+	+	?	+	
7 M 7			+	+	+	+	+	+	
16 M 38	+	+	+		+?	+			R+L
18 F 6	+?	+	+	+	+?	+			
23 M 67		+	+	+	+	+			R+L
9 M 13	+	+	+	+	+		?	+	R+L
30 M 42	+	+	+	+	+	+			
2 M 6	+	+	+	+	+	+	+	+	
12 M 16	+	+	+	+	+	+	+		
3 M 27	+	+	+	+	+	+	+++	+	
8 M 44	+	+	+	+	+	+	++++		R
6 M 33	+	+	+	+	+	+	+++++		R+L
25 F 20	+	+	+	+	+	+	+++++++++		
10 F 21	+	+	+	+	+	+	+++++++++		

+ indicates the presence of definite abnormality. ? indicates abnormality suspected or intermittently present. Optokinetic abnormalities are shown for binocular and monocular viewing with drum motion to the left (L), and right (R). Derangements of response include slow phase of nystagmus in the opposite direction to stimulus motion or lack of modulation of the slow phase velocity of the nystagmus response by changes in the stimulus velocity (this criterion includes, e.g. persistent low velocity nystagmus in response to all stimuli or very high velocity nystagmus provoked by the slightest movement of the drum. Optokinetic abnormalities underlined conform to the primitive pattern of temperonasal > nasotemporal asymmetry Saccadic square-wave intrusions are shown by their predominant rightwards, leftwards directionality.

to establish as scale of how much they were in evidence. This scale is shown in Table 2 by the number of plus signs ascribed to a feature. For non-parametric statistical analysis each plus sign was given the value 1. A question mark was assigned the value 0.5. Amblyopia was assigned 0 if acuity was more than 6/18 and 1 if less than 6/18. Square waves were awarded 1 for each right or left direction in which they presented, 0 if absent.

On Spearman rank correlation there was a positive and significant correlation between severity of OKN abnormalities and the presence of CN-type waveforms; $r = 0.46$; $P = 0.005$ which was attained both with and without the inclusion of the two subjects who had CN on lateral gaze. However, it should be stressed that despite this group association, at least four patients with no evidence of CN in their eye movement recordings had deranged optokinetic responses for all or most viewing conditions.

Optokinetic abnormalities were unrelated to the presence of severe amblyopia, Mann-Whitney U test, $U = 88.8$; $P = 0.8$ or to the presence of square-wave intrusions, Kruskal Wallace ANOVAR by ranks, $H(2) = 0.016$; $P = 0.99$.

On the Mann-Whitney U test the presence of CN-type waveforms was unrelated to amblyopia, $U = 68.5$; $P = 0.24$ or to the presence of square-wave intrusions; $U = 78$; $P = 0.57$.

The presence of a marked amblyopia (11 patients) and the occurrence of square-wave intrusions (11 patients) tended to be mutually exclusive, Mann-Whitney U test, $U = 49$; $P = 0.04$. Only one patient had both.

DISCUSSION

Theories of the origin of LN

Some theories of LN (e.g. Tychsen and Lisberger, 1986; Kommerell, 1988) propose that strabismus and LN are a consequence of the normal physiological temperonasal > nasotemporal preponderance of optokinetic following seen in the neonate before the development of binocular vision (Atkinson and Braddick, 1981; Naegele and Held, 1982). If binocular vision fails to develop, each eye experiences a persistent nasalwards tonus via the asymmetrical optokinetic stimulation which eventually results in convergent strabismus. When one eye is viewing, the tonus is unopposed and becomes manifest as the slow phase of LN. As an additional factor there may be a cortical impairment of temporally directed motion detection (Norcia *et al.*, 1991). This theory accepts a basic (genetic) defect, originally postulated by Worth in 1908 as 'congenital absence of the fusion faculty', but emphasizes ontogenetic factors in the evolution of the various features as a Chevasse's theory of 1939 'structural development on one hand and the rewards of use on the other' (*see* Lyle, 1950).

A different kind of theory which specifically addresses the mechanism of the nystagmus proposes that LN arises due to problems with egocentric direction, visual field direction and the positions of the eyes (Dell'Osso *et al.*, 1979; Abadi, 1980; Dell'Osso and Daroff, 1981). Dell'Osso's explanation is the more specific: normally a target is perceived as 'straight ahead', although there is a net vergence between the two eyes. Upon covering one eye the vergence becomes apparent in that the target is displaced nasalwards with respect to the seeing eye although it is still egocentrically in the same place. In LN these relationships are misinterpreted. When one eye is covered, an inappropriate nasalwards tonus is exerted on the eyes (with respect to the seeing eye) which causes nystagmus.

Evidence against strabismus and LN being caused by optokinetic asymmetry is the number of dissociations and lack of consistent proportional relationships between these features. The optokinetic responses in LN can vary from being normal to apparently absent or 'inverted'. Although all patients with LN have strabismus or unstable phoria (Dell'Osso *et al.*, 1979, 1983*b*) some manage their phorias well (patient 6 who only had LN and strabismus on vergence). Failure of BV is also not a necessary condition for LN since a rare patient with strabismus can have BV (patient 25) and subjects with unstable phoria have useful BV as shown by their rapid recovery of orthotropia when cover is removed. Some of our subjects with LN had familial strabismus with parent and siblings without nystagmus (Table 1).

Our findings favour an alternative theory to optokinetic asymmetry as a cause of LN. It is well known that strabismus and CN can be familial and eight of our patients had parent and siblings with strabismus, both with and without nystagmus. This strong element of inheritance together with the dissociations to be found between the various oculomotor abnormalities in LN are in favour of them being variable genetic expressions as proposed by Jung and Kornhuber (1964). In addition, some cases may be due to acquired embryological disorders involving mechanisms similar to inherited disorders.

If problems with egocentric direction are the specific mechanism of LN, one might expect that possible confusion between eye, target and egocentric direction to be minimal with far targets and enhanced with near targets requiring greater vergence. In support of this notion it is of note that the LN in patients 6 could only be provoked when there was some degree of vergence. Incidentally, there appear to be no studies of the intensity of LN with respect to various target distances and positions of the eyes in the orbit to provide evidence for a more detailed theory of LN. An analogous mechanism is proposed for saccadic instabilities as discussed below.

Nature of OKN responses

The optokinetic disorders in LN are more complex than hitherto described. In particular, as shown in Table 2, nasotemporal asymmetry which has been associated with LN (Kommerell and Mehdorn, 1982; Tychsen *et al.*, 1985; Hatayama *et al.*, 1986; Tychsen and Lisberger, 1986) is not the norm.

In the simplest case the optokinetic response is totally absent or has a normal configuration but only achieves low velocity. In these cases a high velocity spontaneous nystagmus was not present, so there was adequate retinal stimulation and opportunity to observe responsivity over a wide range of velocities. This means that a well-formed but low velocity response suggests a direct impairment of optokinetic performance. It has been proposed that this is the result of an impaired velocity signal in visuo-parietal cortex (Norcia *et al.*, 1991). For example, a poor response to a temporally directed stimulus to the right eye could be ascribed to a lesion affecting the velocity input from temporal retina to the right visuo-parietal cortex. This hypothesis awaits psychophysical testing but is corroborated by preliminary studies on movement evoked visual evoked potentials (Norcia *et al.*, 1991).

In some patients the onset of an optokinetic stimulus triggered a nystagmus which thereafter was not modulated by the velocity or direction of the stimulus. Such nystagmus may be a system instability provoked by the moving visual field as suggested by Dickinson and Abadi (1990). The underlying optokinetic response may be weakly intact but is masked or even adapted out (Dickinson and Abadi, 1990).

Amongst the more striking abnormalities were nystagmic responses whose slow phase directions were dependent upon the position of the eyes in the field of gaze (e.g. Fig. 4). This type of 'reversed' or 'wrong way' response was observed by Tychsen and Lisberger (1986) during pursuit tasks. These authors associated the phenomenon with low velocity target motion which was not always the case with our patients. In extreme cases the slow phases were of higher velocity than the stimuli (either in the same or opposite directions). Occasionally responses could oscillate in direction, apparently as a function of stimulus velocity (Figs 3, 4). Such abnormalities are similar to those in fully developed CN (Halmagyi *et al.*, 1980). In CN, pursuit (Dell'Osso, 1986; Kurzan and Buttner, 1989) and optokinetic signals (Kurzan and Buttner, 1989) may be intact but are masked by, or adapted in, the presence of the nystagmus. The result is that they may have velocities which are abnormally high or 'inverted' depending upon how the stimulus affects the null point of the nystagmus.

Although the more deranged optokinetic responses tended to occur when there was also congenital type nystagmus (Table 2), occasional patients with no evidence of CN-type waveforms in their recordings had marked derangements (e.g. Figs 2, 3; patient 13). One must conclude that responses with slow phase velocities greater than the stimulus or apparently inverted in direction are likely to be related to CN mechanisms even when an explicit CN waveform is not evident.

In summary, there are two likely mechanisms for abnormal optokinetic responses in subjects with LN: (i) degradation of visual motion signals in the cortex; (ii) masking of the optokinetic response with the mechanisms of both LN and CN.

Relationship between mechanisms of LN and CN and optokinetic responses

Patients with pure LN do not have evidence of derangement of brainstem oculomotor mechanisms. Saccades and the vestibular-ocular reflex (Tychsen *et al.*, 1985) are intact. Many patients have bidirectionally normal pursuit and OKN responses under certain conditions, i.e. with either both eyes or one eye viewing (Tychsen and Lisberger, 1986 and this study). This negative evidence suggests that the disorder underlying LN is at a cortical level. In contrast, it is proposed that CN is caused by positive feedback on the neural velocity-position integrator in the brainstem causing the eyes to drift off target with an increasing velocity (Dell'Osso and Daroff, 1981; Optican and Zee, 1984).

Dell'Osso (1985) estimates that 80% of the nystagmus associated with strabismus is CN, pure LN accounts for 15% with mixtures of the two comprising only 5%. Our sample was biased against CN and so probably corresponds to the categories LN and LN+CN (i.e. 20%). Since more than 50% of our patients were found to have CN features (identified in a wider range of manoeuvres than used in other surveys), possibly up to half of the patients with LN also have some CN. The strong association between LN and CN could be taken to indicate that their underlying genetic or acquired embryological disorders are similar but manifesting in different ways according to expression factors. This view would point to a more unified theory of the aetiology of 'congenital nystagmuses'.

Precisely how the mechanisms of LN and CN interact when both are present is difficult to ascertain. In some cases the CN only appears when there is a strong velocity signal, such as pursuit, which displaces the null sufficiently to reveal the CN. When CN appears on cover testing the nasalwards drift caused by the LN mechanism might trigger the CN instability. Difficulties of interpretation arise because CN itself can have apparently linear, velocity increasing or decreasing slow phases which make proportional classification into LN versus CN hazardous (Dell'Osso, 1985).

Saccadic square-wave intrusions

Subjects with strabismus are known to switch between eyes when viewing to the right and left (Dell'Osso *et al.*, 1983*a*). This results in a saccade which brings the eye selected for viewing into alignment which can be construed as a convenient manoeuvre. We have shown that saccadic instabilities also occur monocularly with the patient trying to remain on target so that nothing is to be gained by switching eyes. There are two alternative explanations. First, because saccadic intrusions did not occur with severe amblyopia, it would appear that two functioning visual fields are necessary to cause the instability. The saccades could be due to the uncertainty about whether to control eye movements with respect to the visual map of the right eye or the left eye. If the maps have an abnormal correspondence with each other and with the positions of the eyes, a shift of control between maps may result in an eye movement. This mechanism is analogous to that hypothesized by Dell'Osso for LN. (ii) Alternatively, although square waves occur in normal subjects and in a variety of diseases (Jones *et al.*, 1983; Abel *et al.*, 1984; Shallo-Hoffmann *et al.*, 1988), those in our patients are most like descriptions of the 'visual grasp reflex' (Sharpe, 1986) and square waves in patients with cortical lesions (Page *et al.*, 1984). Since saccadic instability is a sign of frontal lobe dysfunction (Guitton *et al.*, 1985), the question is raised of whether there is other evidence for frontal lobe abnormalities in these patients.

Implications for clinical neurology

Patients with latent nystagmus may show oculomotor disorders with a similar appearance to those seen in acquired neurological disease. However, if the cardinal components of LN, CN and strabismus or unstable phoria are identified, then one can recognize the various other disorders as attendant features which do not imply the presence of an acquired disorder. Accordingly, it is always of value to examine for LN in any patient who is suspected of having an eye movement disorder. Unfortunately, the interpretation of eye movements in the rare patient who may have LN and an acquired oculomotor disorder may be difficult.

The amplitude of LN and CN may change throughout life (van Weerden and Houtman, 1984; Gresty *et al.*, 1991, three patients studied here), enhancing spontaneously or with trivial disease and minor head injury. Under these circumstances it can become symptomatic and is particularly suggestive of an acquired disease. Identifying the nystagmus as LN or CN may help to obviate extensive investigations.

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COMPARISON OF PREDICTABLE SMOOTH OCULAR AND COMBINED EYE-HEAD TRACKING BEHAVIOUR IN PATIENTS WITH LESIONS AFFECTING THE BRAINSTEM AND CEREBELLUM

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SUMMARY

We compared the ability of eight normal subjects and 15 patients with brainstem or cerebellar disease to follow a moving visual stimulus smoothly with either the eyes alone or with combined eye-head tracking. The visual stimulus was either a laser spot (horizontal and vertical planes) or a large rotating disc (torsional plane), which moved at one sinusoidal frequency for each subject. The visually enhanced vestibulo-ocular reflex (VOR) was also measured in each plane. In the horizontal and vertical planes, we found that if tracking gain (gaze velocity/target velocity) for smooth pursuit was close to 1, the gain of combined eye-hand tracking was similar. If the tracking gain during smooth pursuit was less than about 0.7, combined eye-head tracking was usually superior. Most patients, irrespective of diagnosis, showed combined eye-head tracking that was superior to smooth pursuit; only two patients showed the converse. In the torsional plane, in which optokinetic responses were weak, combined eye-head tracking was much superior, and this was the case in both subjects and patients. We found that a linear model, in which an internal ocular tracking signal cancelled the VOR, could account for our findings in most normal subjects in the horizontal and vertical planes, but not in the torsional plane. The model failed to account for tracking behaviour in most patients in any plane, and suggested that the brain may use additional mechanisms to reduce the internal gain of the VOR during combined eye-head tracking. Our results confirm that certain patients who show impairment of smooth-pursuit eye movements preserve their ability to smoothly track a moving target with combined eye-head tracking.

INTRODUCTION

When we attempt to track visually a smoothly moving object, we may do so either with the eyes alone (ocular tracking) or with a combined movement of the eyes and head (combined eye-head tracking). During combined eye-head tracking, it is necessary to override the vestibulo-ocular reflex (VOR); this reflex acts to stabilize the angle of gaze when head movements occur as a subject fixes upon a stationary visual scene. Failure to 'suppress' the VOR during combined eye-head tracking has been recommended as a useful clinical test to detect, for example, cerebellar dysfunction (Zee, 1977; Dichgans *et al.*, 1978).

Several suggestions have been made as to how the VOR is nulled during combined

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eye-head tracking. First, the VOR signal might be cancelled by another internal signal, such as that responsible for ocular tracking (Barnes *et al.*, 1978; Lanman *et al.*, 1978; Lau *et al.*, 1978). This hypothesis is supported by reports of similar dynamic properties of smooth pursuit and combined eye-head tracking (Barnes *et al.*, 1978; Barnes and Eason, 1988; Barnes and Lawson, 1989). Furthermore, experiments that capitalize on the different latencies to onset of the VOR (less than 16 ms) and ocular tracking (greater than 75 ms), by suddenly 'braking' the head movement during combined eye-head tracking, suggest that an internal ocular tracking signal is active during combined eye-head tracking (Lanman *et al.*, 1978; Leigh and Huebner, 1993).

Other possible ways that the VOR might be modulated during combined eye-head tracking include cancellation by other types of neural signal, such as a head-tracking command (Robinson, 1982), or 'suppression' of the VOR itself. This last suggestion is based on the finding that some reduction of the gain of the VOR may be achieved by the mental image of the individual (Barr *et al.*, 1976). For example, if subjects imagine an earth-fixed target during rotation in darkness, VOR gain is close to 1; however, if the subjects imagine a target rotating with them, VOR gain falls to about 0.4. Such lowering of the gain by a mental image might contribute to a reduction of the VOR achieved during combined eye-head tracking.

We have previously compared horizontal smooth-pursuit eye movements and active, combined eye-head tracking in normal subjects and in patients with peripheral vestibular deficiency (Leigh *et al.*, 1987). A simple model (Fig. 1), in which an internal ocular tracking signal cancelled the VOR, accounted well for the behaviour of both our subjects

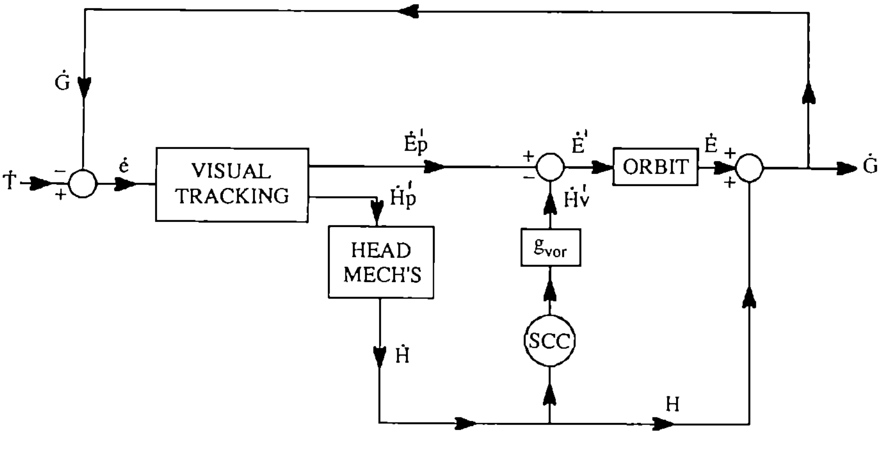

FIG. 1. A simple model to account for combined eye-head tracking, ocular tracking and the visually enhanced VOR. Target velocity ($\dot{T}$) is compared with gaze velocity ($\dot{G}$) at the retina (summing junction at left). Retinal error velocity ($\dot{e}$) is the input to visual tracking mechanism (which has an internal gain, K, for ocular tracking; *see* Methods for derivation); this mechanism synthesizes command signals for eye velocity ($\dot{E}'_p$) and head velocity ($\dot{H}'_p$). The latter acts upon head mechanics (HEAD MECH'S) to cause a head rotation with velocity $\dot{H}$, which stimulates the VOR via the semicircular canals (SCC). The output of the SCC is influenced by the internal gain of the VOR (g_{vor}), and the resulting signal, $\dot{H}'_v$, the vestibular system's estimate of head velocity sums with $\dot{E}'_p$. Thus, at this internal summing junction, the ocular tracking command signal, $\dot{E}'_p$, 'cancels' (partially or completely) the VOR signal, $\dot{H}'_v$, the result is an eye movement command signal, $\dot{E}'$, which acts on the orbital mechanics (ORBIT) to produce an eye rotation with velocity $\dot{E}$. Finally, $\dot{H}$ sums with $\dot{E}$ to produce $\dot{G}$. (Adapted from Leigh *et al.*, 1987.)

and patients. Other reports, however, have described patients with lesions of the central nervous system who showed different deficits of ocular tracking and combined eye-head tracking, such that a simple cancellation model could not account for their tracking behaviour (Chambers and Gresty, 1983; Ranalli and Sharpe, 1988).

In this study, we set out to compare ocular tracking and combined eye-head tracking in the horizontal, vertical and torsional planes in normal subjects and in patients with brainstem or cerebellar disease which are known to impair ocular tracking. In making this comparison, it should be noted that in the horizontal and vertical planes, ocular tracking of a small, moving target is due to the smooth-pursuit eye movement system. In the torsional plane, however, ocular tracking can only be induced by large-field stimuli which rotate around the line of sight to induce torsional optokinetic nystagmus (OKN). Thus our strategy was to test the model shown in Fig. 1 separately, in each plane, for each subject or patient.

METHODS

Selection of patients

We studied 15 patients (P1–P15), age range 35–79 yrs, with disorders affecting vertical or horizontal ocular tracking eye movements, identified during clinical examinations (Table 1). These included four patients with one of the following conditions: Parkinson's disease, progressive supranuclear palsy and cerebellar disease. In addition, we studied three patients with other degenerative conditions: one with cortical-basal ganglionic degeneration, and two patients with undiagnosed progressive disorders characterized by parkinsonian features and dystonic postures. All patients were alert, able to cooperate with testing and gave informed consent.

Our strategy was to use data from each patient as an independent test of the model shown in Fig. 1. However, because of the diverse clinical nature of the patients studied we also studied a group of control subjects. The latter consisted of eight healthy, normal subjects (seven male, one female), of ages 29, 32, 42, 44, 52, 54, 69 and 71 yrs, who are referred to, consecutively, as S1–S8. All subjects also gave informed consent. No normal subject was taking medication. Only one subject had more than two diopters refraction (five diopters, contact lenses); during testing no subjects wore their correction lenses.

Recording methods and test stimuli

Horizontal, vertical and torsional gaze and head rotations were measured using the magnetic search coil technique (Ferman *et al.*, 1987). Patients and subjects wore a search coil on their dominant eye; the other was patched whenever there was any doubt about conjugacy They also wore a similar search coil firmly attached to their foreheads to measure head position. Search coils were calibrated prior to each experimental session using a protractor device attached to the vestibular chair. Subjects sat upright in a stationary chair, and during ocular tracking braced their heads against a headrest. During test condition A–F (*see below*), they viewed a spot of red light projected from a laser onto a tangent screen at a viewing distance of 1.3 ms. During conditions G–I, they viewed a circular visual display of random dots at a distance of approximately 50 cm that subtended a visual angle of ±45 deg. The motor which rotated the circular display about the line of sight of the subject was controlled according to test conditions. During condition G, a function generator was used to produce the optokinetic stimulus. During condition H, an amplified torsional head-coil signal was used to rotate the visual display at the same angular speed as the subject's head. During condition I, no voltage signal was fed to the motor. The nine test conditions each lasted for 20 s. Prior to starting these tests, patients were asked to view the laser spot that was initially stationary at the zero (straight ahead) position, and then stepped through ±15 deg, in a predictable pattern, first horizontally and then vertically. In this way we measured fixation behaviour and saccades of up to 30 deg amplitude. The test conditions were as follows.

A, ocular tracking of a target moving horizontally on the tangent screen, sinusoidally, at approximately 0.5 Hz through ±15 deg.

TABLE 1. SUMMARY OF CLINICAL FEATURES OF PATIENTS STUDIED

No.	*Age (yrs)/sex*	*Diagnosis*	*Duration (yrs)*	*Medication*
1	63/M	PD, epilepsy	5	L-dopa/carbidopa, carbamazepine
2	77/M	PD	15	Selegiline, parsidol
3	64/F	PD	8	L-dopa/carbidopa, pergolide
4	63/M	PD, bilateral hemisphere strokes	5	L-dopa/carbidopa, trihexyphenidyl, desipramine
5	67/F	PSP, hypertension	2	Lisinopril
6	79/F	PSP, left hemisphere stroke	4	None
7	72/F	PSP	5	L-dopa/carbidopa, amitriptyline
8	69/F	PSP	3	Amitriptyline, captopril
9	60/M	Cerebellar atrophy	8	Propranolol, trihexyphenidyl
10	42/F	Cerebellar degeneration	8	None
11	61/M	Cerebellar degeneration, epilepsy	3	Phenytoin
12	37/F	Cerebellar degeneration	15	None
13	35/F	Undiagnosed, dystonia and parkinsonism	4	None
14	58/F	Undiagnosed, parkinsonism	5	L-dopa/carbidopa, phenytoin
15	73/F	CBGD	6	Temazepam

CBGD = Cortical-basilar ganglionic degeneration; PD = Parkinson's disease; PSP = progressive supranuclear palsy.

B, active, head-free combined eye-head tracking of a target moving horizontally on the tangent screen, sinusoidally, at approximately 0.5 Hz through ±15 deg.

C, active horizontal head rotations, approximately sinusoidal, at about 0.5 Hz through about ±15 deg as the subject attempted to view the stationary target located at 0 deg.

D, ocular tracking of a target moving vertically on the tangent screen, sinusoidally, at approximately 0.5 Hz through ±15 deg.

E, active, head-free combined eye-head tracking of a target moving vertically on the tangent screen, sinusoidally, at approximately 0.5 Hz through ±15 deg.

F, active vertical head rotations, approximately sinusoidal, at about 0.5 Hz through about ±15 deg as the subject attempted to view the stationary target located at 0 deg.

G, with the subject's head stationary, the circular visual display moved sinusoidally at 0.5 Hz, through an amplitude of ±15 deg.

H, active head rotation in roll (torsional plane), approximately sinusoidal, at about 0.5 Hz through about ±15 deg, while viewing the circular visual display which moved synchronously and equally with the subject's head.

I, active head rotations in roll, approximately sinusoidal, at about 0.5 Hz through about ±15 deg, while viewing the stationary visual display.

All active head rotations were cued by a metronome; in those individuals who had difficulty in doing this, even after coaching (e.g. patients with progressive supranuclear palsy), the investigator aided with passive movements. For normal subjects as a group, the mean frequency and peak-to-peak amplitude of head movements during VOR were 0.52 Hz and 32.6 deg, respectively, being similar in all three planes. For the patients as a group, the mean frequency of head movements during VOR was 0.56 Hz, being similar for all planes, but mean peak-to-peak amplitude ranged from 21.9 deg torsionally to 26.6 deg horizontally. Patients were actively encouraged to follow the moving target during ocular tracking and combined eye-head tracking. Rather than testing the VOR in darkness, during which the mental state of some patients might be difficult to control, we measured the gain of the visually enhanced VOR. Although normal subjects were able to track the visual target moving at a frequency of 0.5 Hz, some patients were unable to generate appreciable smooth eye movements at this frequency. Therefore, our strategy was to reduce the frequency of the target motion to a value at which some smooth ocular tracking was possible (as low as 0.27 Hz), but to then hold the stimulus frequency constant for testing of ocular tracking and combined eye-head tracking for each patient, for each plane.

Data collection and analysis

Gaze, head and visual display signals were digitized at 200 Hz, following analogue filtering (Krohn-Hite Butterworth filters, bandwidth 0–90 Hz). Responses from each subject were analysed interactively (Hary *et al.*, 1987).

Eye position in the orbit was obtained by first subtracting head from gaze. Because the axes of rotation of the head and of the eye in the orbit differ, we made a small correction to the combined eye-head tracking and VOR data so that a direct comparison could be made between the different test paradigms. For the horizontal plane, in normal subjects, we used a geometric correction based on measurements of the eye and head geometry of each individual subject (Huebner *et al.*, 1992). Because this procedure requires the subject to align the angle of gaze with two visual targets (necessitating steady fixation), we could not reliably perform it in our patients. Instead, we used a simplification of this correction:

$$E_C = E_M * \frac{1}{(1+R/D)}$$

where E_C = corrected eye rotation in orbit, E_M = measured eye rotation in orbit, R = radius of rotation of eyes in head (i.e. distance from centre of rotation of head to the eyes, assumed to be 10 cm), and D = distance from centre of rotation of head to target (1.3 m). This simplification, which is discussed further in the paper by Huebner *et al.* (1992), does not take into account the individual's head geometry (radius of rotation of eyes in head and interocular separation) or the fact that our screen was flat rather than cylindrical. Nonetheless, in preliminary experiments in two normal subjects, we found that, for our viewing distance of 1.3 m, this simple correction gave very similar results to the more complicated geometric correction in these subjects and, furthermore, it also gave appropriate results during vertical head movements. Therefore, we used the simple correction in the horizontal plane for our patients and in the vertical plane in both subjects and patients.

To measure the tracking gain (gaze velocity/target velocity), we first inspected records to confirm that there was minimal phase shift between gaze and target signals. Data were then differentiated using a two-point central-difference algorithm, to give gaze velocity ($\dot{G}$) and head velocity ($\dot{H}$); eye-in-orbit velocity ($\dot{E}$) was obtained by subtracting $\dot{H}$ from $\dot{G}$. We than used an interactive desaccading procedure (Barnes, 1982) and finally estimated tracking gain of the remaining points (typically 2000 for each variable per trial) using a linear regression technique. In preliminary experiments, we used a coherence procedure to confirm the validity of this method (Bendat and Piersol, 1986). The gain values of the optokinetic response (gaze velocity/stimulus velocity), and of the visually enhanced VOR (eye-in-orbit velocity/head velocity), were calculated in a similar manner. In some subjects and patients, mild asymmetries of the horizontal and vertical responses were evident; we found, however, that measuring the gain of the overall response did not produce different results from analysing responses in each direction separately.

Because our patients with cerebellar disease showed gaze-evoked nystagmus, we also made an estimate of tracking gain during ocular tracking and combined eye-head tracking by averaging at least 10 measurements of tracking gain (made interactively) as the patients' eyes passed through primary position. Comparison was then made using Wilcoxon's test.

Use of data to test hypotheses

To test the model shown in Fig. 1, we used algebraic equations previously described (Leigh *et al.*, 1987). First, the value of the internal gain of the 'visual tracking' mechanism, K, was calculated from the measured tracking gain during ocular tracking ($\dot{G}/\dot{T}$) using:

$$K = \frac{(\dot{G}/\dot{T})}{[1-(\dot{G}/\dot{T})]}$$

Secondly, the value of g_{vor} (which represents the sum of vestibular and other non-visual mechanisms contributing to the generation of compensatory eye movements during active head rotations) was calculated from the measured gain of compensatory eye movements ($\dot{E}/\dot{H}$) during active head movements, as the subject fixated the stationary target (visually enhanced VOR), using:

$$g_{vor} = -\frac{\dot{E}}{\dot{H}} - \frac{K(\dot{E}+\dot{H})}{\dot{H}}$$

Finally, using K, g_{vor}, peak target velocity ($\dot{T}_p$) and the average value of peak head velocity ($\dot{H}_{ap}$), which was measured during combined eye-head tracking, the model's prediction of tracking gain during combined eye-head tracking was calculated using:

$$\text{Predicted combined eye-head tracking gain} = \left[K+\dot{H}_{ap}\frac{(1-g_{vor})}{\dot{T}_p}\right] * \frac{1}{(1+K)}$$

A comparison of predicted and observed combined eye-head tracking gain was then made for each subject and patient.

RESULTS

The gain values of ocular tracking, combined eye-head tracking and visually enhanced VOR, for each subject and patient, in each plane of testing, are summarized below and in the three panels of Fig 2.

Comparison of ocular tracking and combined eye-head tracking in the horizontal plane

Of the normal subjects, five (S1, S3 – S6) showed gain values that were similar (i.e. within 5%) during ocular tracking and combined eye-head tracking; all five had ocular tracking gain values greater than 0.9. An example of this behaviour and the corresponding visually enhanced VOR is shown in Fig. 3A,C,E. The remaining three normal subjects (S2, S7, S8) all showed gain values that were more than 10% greater for combined eye-head tracking than ocular tracking; all had gain values for ocular tracking of less than 0.75. An example is shown in Fig. 4, left-sided panels. The gain of the visually enhanced VOR in the normal subjects ranged from 0.94 to 1.03. During combined eye-head tracking, the mean (±SD) of the ratio of average, peak head velocity to peak target velocity, for the normal subjects as a group, was 1.22 (0.34).

Of the patients, four (P3, P4, P13, P15) showed gain values within 10% of each other during ocular tracking and combined eye-head tracking; all had tracking gain values during ocular tracking exceeding 0.8. On the other hand, 10 patients (P1, P2, P5 – P11, P14), including individuals from all diagnostic groups, showed larger gain values during combined eye-head tracking than during ocular tracking; all had ocular tracking gain values of less than 0.6 (Fig. 3B,D,F). In two patients (P2, P3), a strategy of sometimes using anticipatory saccades to track the target (apparent in Fig. 3B) may have contributed to the lower gain during ocular tracking. In cerebellar patients P9 – P11, mean tracking gain measured as the eye passed through the primary position was significantly greater ($P < 0.05$) during combined eye-head tracking than during ocular tracking. Only P12 showed a greater gain value during ocular tracking than during combined eye-head tracking; she was also notable for a visually enhanced VOR gain of 1.11 (Fig. 4, right-sided panels). Other patients either showed gain values for their visually enhanced VOR that were close to unity or were low (especially the cerebellar patients). During combined eye-head tracking, the mean (±SD) of the ratio of average peak head velocity to peak

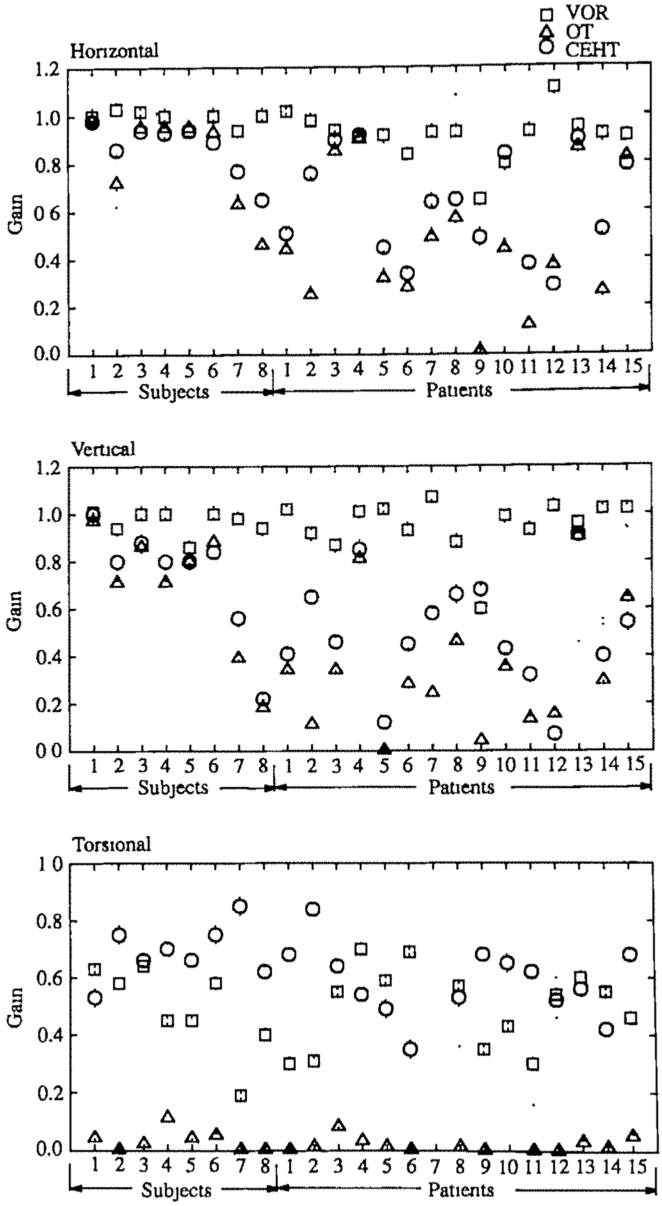

FIG. 2. Summary of gain values of ocular tracking (OT), combined eye-head tracking (CEHT) and visually enhanced VOR for each subject and patient, in each of the planes tested.

target velocity was 0.93 (0.24) for parkinsonian patients, 0.94 (0.22) for patients with progressive supranuclear palsy, 1.64 (0.45) for cerebellar patients and 0.97 (0.25) for the patients with miscellaneous degenerative conditions.

When these data were used to test the model shown in Fig. 1, the predicted combined

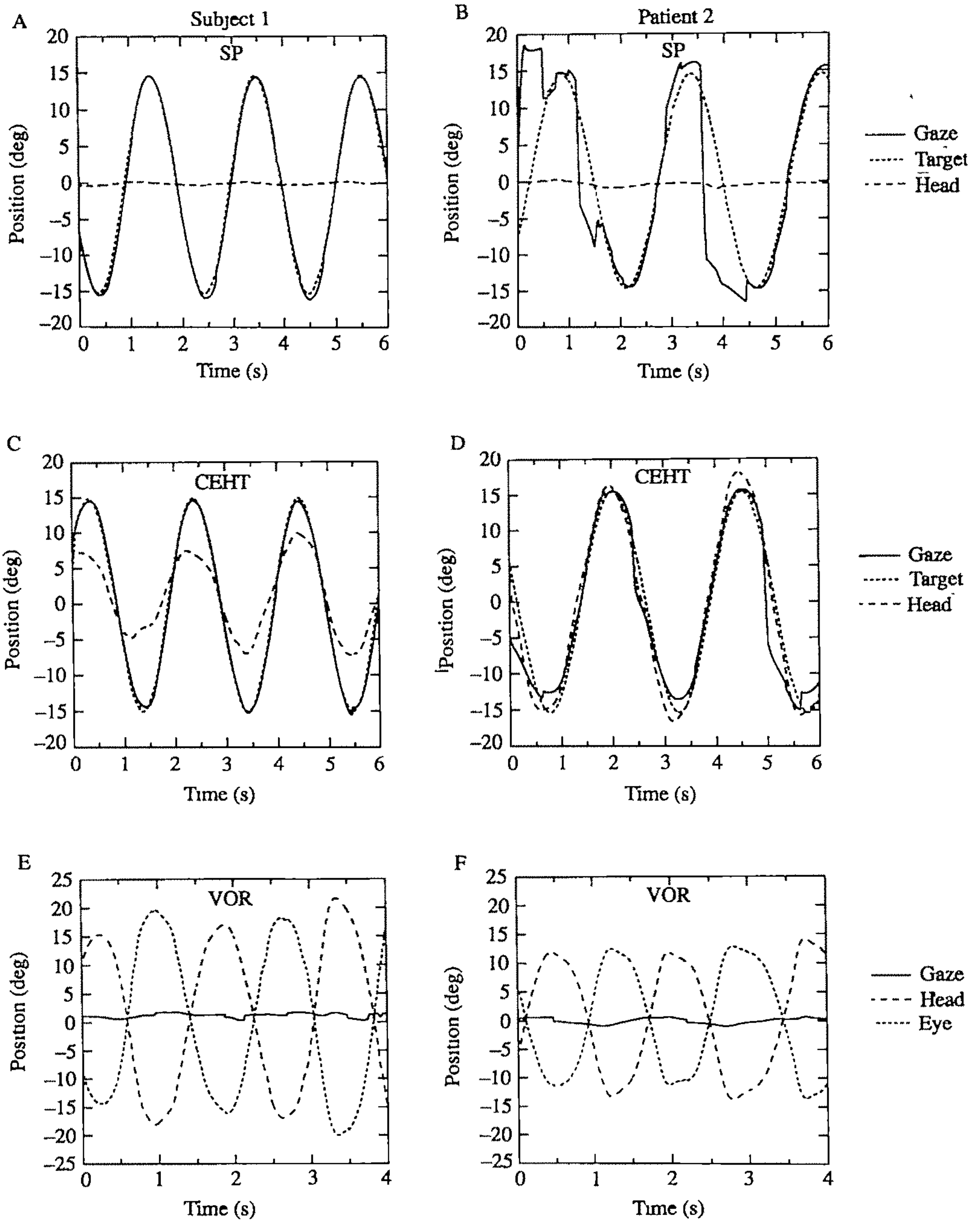

FIG. 3. A comparison of ocular tracking [smooth pursuit (SP)], combined eye-head tracking (CEHT), and the visually enhanced VOR in the horizontal plane. Panels A, C and E are from S1; panels B, D and F are from P2, who has Parkinson's disease The normal subject shows similar tracking (gain close to 1) during both ocular tracking and combined eye-head tracking. The patient, however, tracks better (higher gain) during combined eye-head tracking than during ocular tracking; sometimes he uses a strategy of generating saccades that anticipate the target's movement. The visually enhanced VOR gain in both the patient and the subject are approximately 1.

eye-head tracking gain was within 10% of the measured value for six of the eight normal subjects (Fig. 5, top panel); the exceptions (S2 and S8) both showed higher observed gain values for combined eye-head tracking than predicted. In contrast, the predicted combined eye-head tracking gain was within 10% of observed values in only eight of the 15 patients (P3–P5, P8–P10, P12, P13). Five patients (P1, P2, P7, P11, P14) showed observed combined eye-head tracking gain values that were greater than predicted by the model; in two patients (P6, P15) observed values of combined eye-head tracking gain were less than predicted. In the case of P12, whose visually enhanced gain was 1.11, the model correctly predicted the gain of her combined eye-head tracking.

Comparison of ocular tracking and combined eye-head tracking in the vertical plane

Of the normal subjects, three (S1, S3, S5) showed gain values that were within 5% of each other during ocular tracking and combined eye-head tracking; an additional three subjects (S2, S4, S6) showed gain values that were within 10% of each other. An example and the corresponding visually enhanced VOR is shown in Fig. 6A,C,E. The values of ocular tracking gain were generally smaller than in the horizontal plane, especially in the older subjects. The gain of the visually enhanced VOR in the normal subjects was within 6% of that required for perfect compensation, except for S5; in this case some discomfort from the eye search coil (which she subsequently commented on) may have distracted her during this trial. During combined eye-head tracking, the mean (±SD) of the ratio of average peak head velocity to peak target velocity for the normal subjects as a group was 1.04 (0.20).

Of the patients, only two (P4, P13) showed gain values during ocular tracking and combined eye-head tracking that were within 10% of each other. Eleven patients (P1–P3, P5–P11, P14) showed combined eye-head tracking that was superior to ocular tracking; this was the case in patients from all four diagnostic groups, but was most evident in those with progressive supranuclear palsy, who were unable to supplement their ocular tracking with saccades. An example from a patient with progressive supranuclear palsy is shown in Fig. 6B,D,F. Two patients (P12, P15) showed greater gain values during ocular tracking than during combined eye-head tracking. The gain of ocular tracking was generally lower than in the horizontal planes, especially for the patients with cerebellar disease or progressive supranuclear palsy. All but three patients (P3, P8, P9) showed gain values for their visually enhanced VOR that were within 10% of that required for perfect compensation; none showed elevated values. During combined eye-head tracking, the mean (±SD) of the ratio of average peak head velocity to peak target velocity was 0.81 (0.15) for parkinsonian patients, 0.71 (0.21) for patients with progressive supranuclear palsy, 1.43 (0.45) for cerebellar patients and 0.91 (0.21) for the patients with miscellaneous degenerative conditions.

When these results were used to test the model shown in Fig. 1, the predicted combined eye-head tracking gain was within 10% of the measured value for five of the normal subjects (Fig. 5, middle panel); of the exceptions, two (S5, S8) showed lower gain values, and one (S7) showed a greater gain value for observed combined eye-head tracking than predicted. In the patients, predicted combined eye-head tracking gain was within 10% of the observed values in only five (P3, P4, P8, P9, P13) of the 14 patients in whom the model could be tested. Seven patients (P1, P2, P6, P7, P10, P11, P14) showed larger measured gain values than predicted. The two patients (P12, P15) who showed ocular tracking that was superior to combined eye-head tracking, also had higher gain values for predicted than observed combined eye-head tracking.

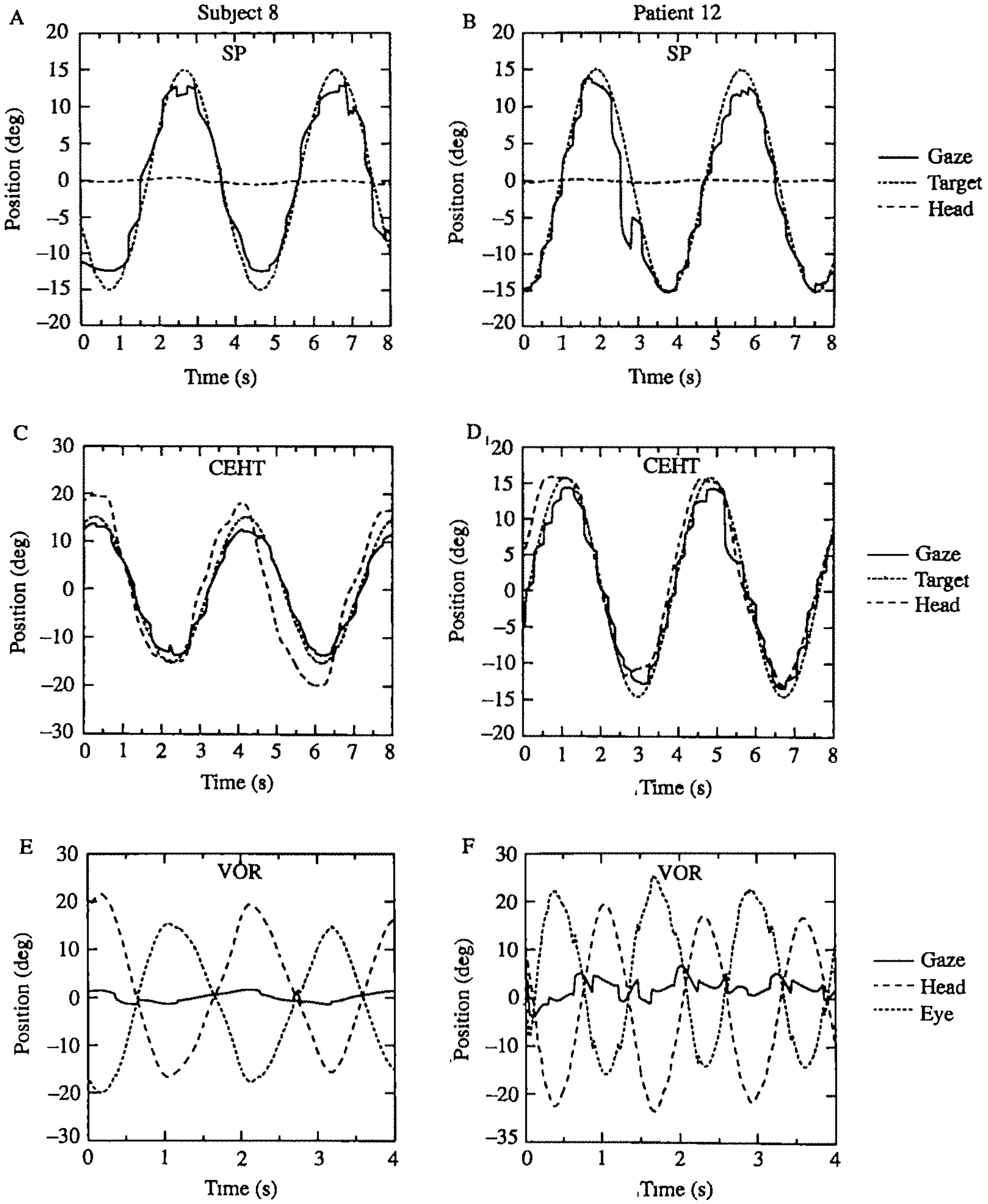

FIG. 4A—F.

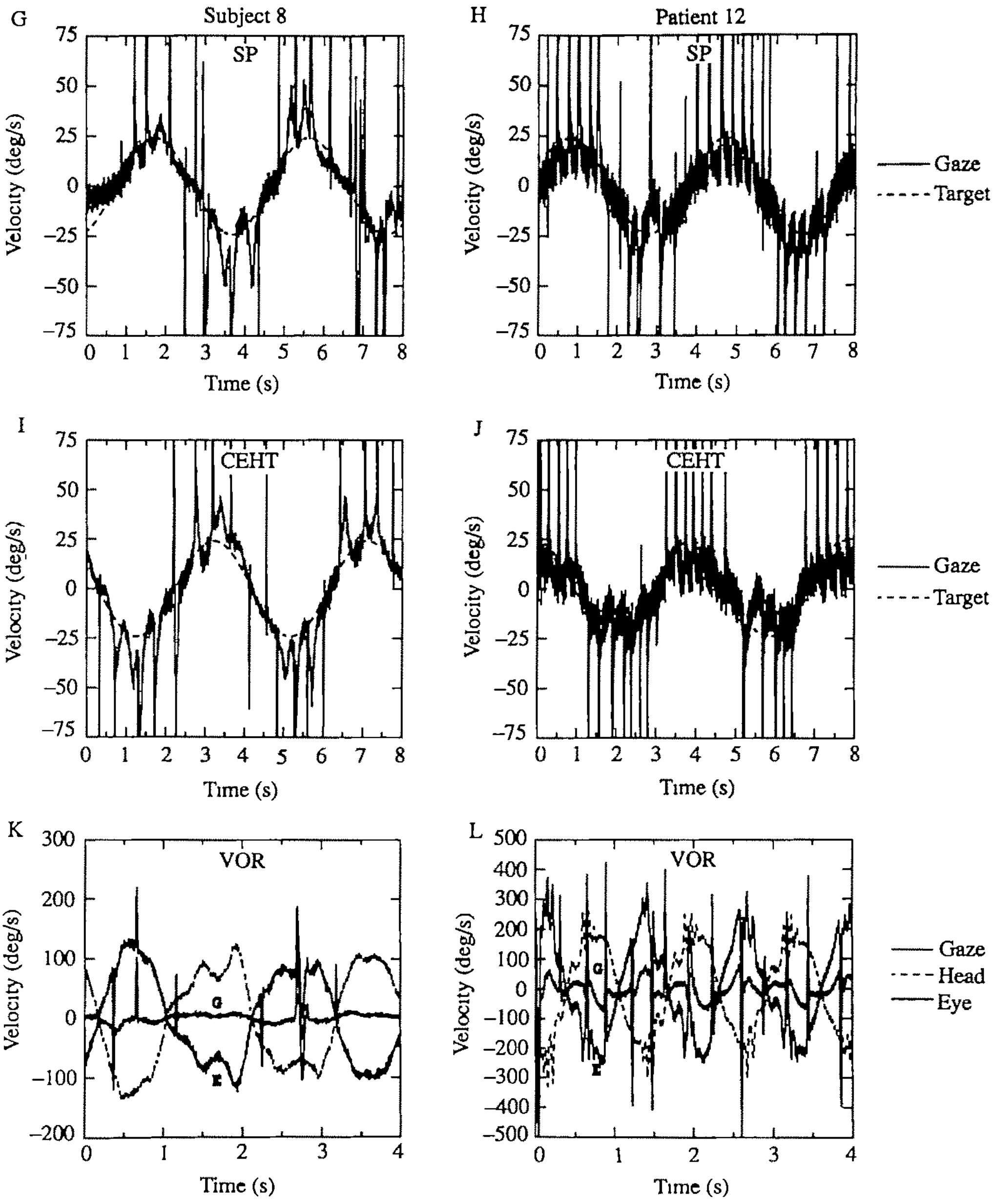

FIG. 4. A comparison of ocular tracking [smooth pursuit (SP)], combined eye-head tracking (CEHT), and the visually enhanced VOR in the horizontal plane. Panels A–F are position records; panels G–L are corresponding velocity records. For clarity of display, head movements are shown only in the position records of SP and combined eye-head tracking Panels on the left (A, C, E, G, I, K) are from S8, an elderly normal subject; panels on the right (B, D, F, H, J, L) are from P12, who has cerebellar degeneration. The normal subject showed impaired ocular tracking (gain 0.47) but somewhat better combined eye-head tracking (gain 0.65). The gain of his visually enhanced VOR was 1 The patient, however, showed marginally better ocular tracking (gain 0.38) than combined eye-head tracking (gain 0.29); the gain of her visually enhanced VOR was 1.11, necessitating 'back-up' corrective saccades. In panels K and L, G indicates gaze velocity, and E indicates eye velocity. Note that saccades were removed from velocity data before gain values were calculated (*see* Methods).

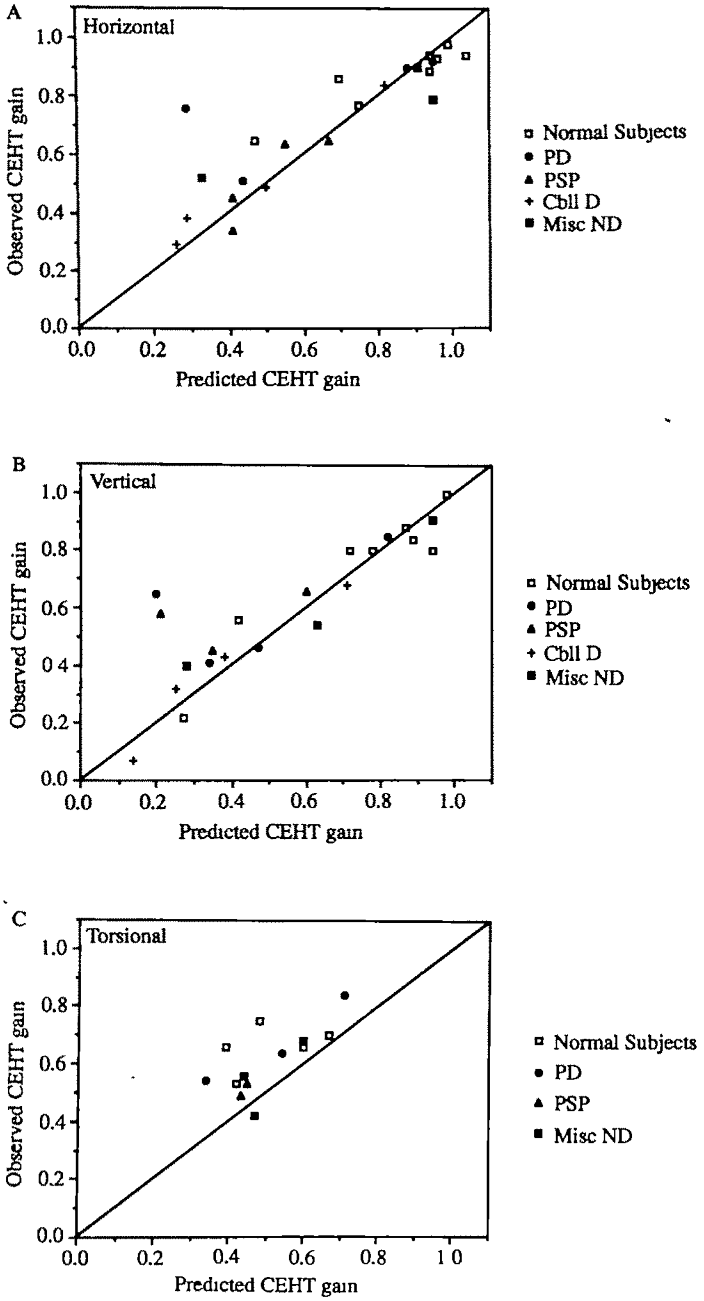

FIG. 5. A comparison of the measured values of combined eye-head tracking (CEHT) gain and those predicted from the model shown in Fig. 1 for (A) horizontal, (B) vertical and (C) torsional planes. The solid line corresponds to exact predictions of observed data by the model. Note that, in A and B, data points from most normal subjects lie close to the solid line but many data points from patients lie above the line, indicating that observed gain values for combined eye-head tracking were greater than predicted by the model. In C, most data from subjects and patients lie above the solid line, indicating that the model systematically underestimates the observed values of combined eye-head tracking gain.

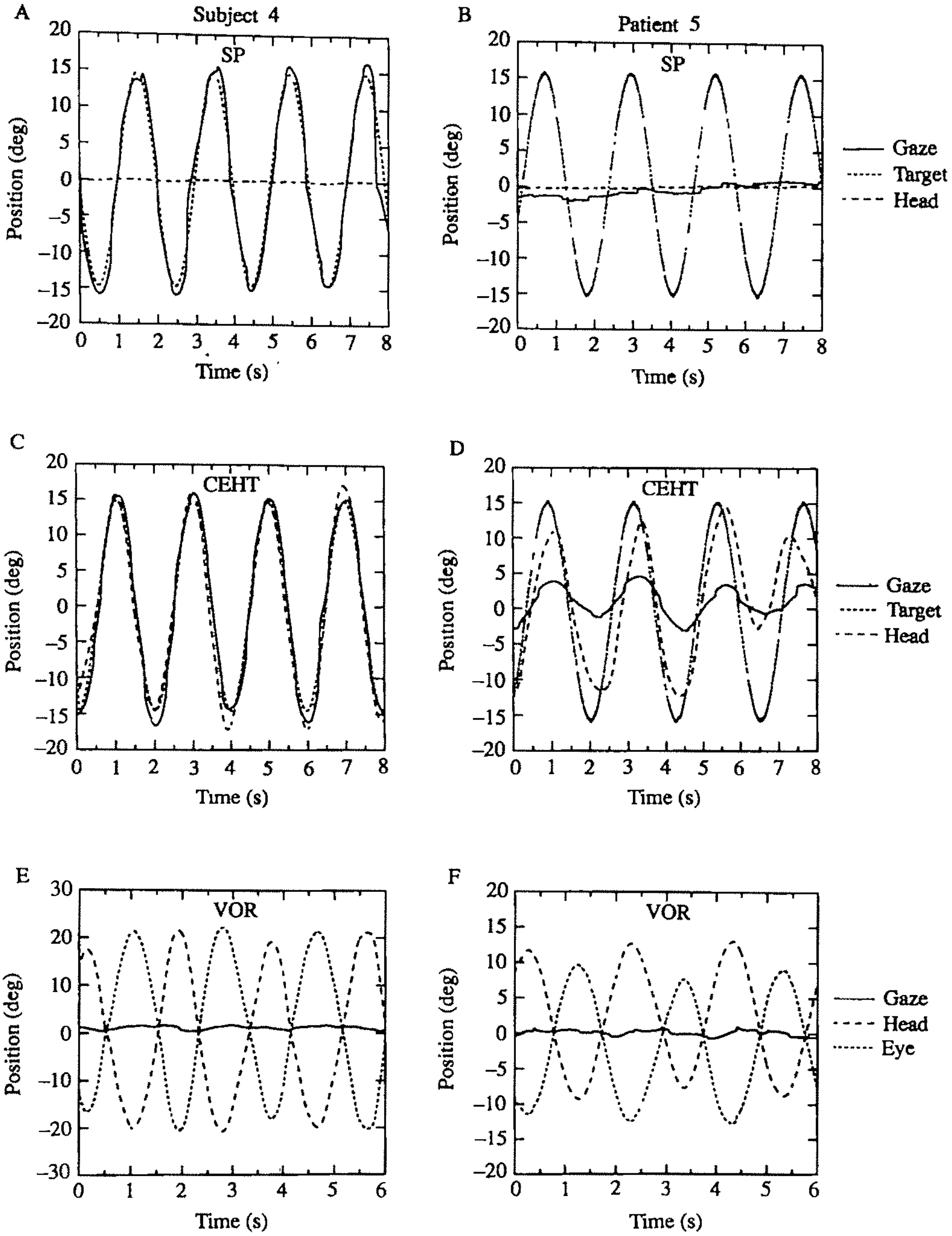

FIG. 6. A comparison of ocular tracking [smooth pursuit (SP)], combined eye-head tracking (CEHT), and the visually enhanced VOR in the vertical plane. Panels A, C and E are from normal subject S4; panels B, D and F are from P5, who has progressive supranuclear palsy The normal subject shows similar tracking (gain close to 1) during both ocular tracking and combined eye-head tracking. The patient, however, tracks much better (higher gain) during combined eye-head tracking than during ocular tracking; this difference is emphasized by her inability to make corrective vertical saccades. The gain of the visually enhanced VOR in both the patient and the subject are approximately 1.

Comparison of ocular tracking and combined eye-head tracking in the torsional plane

All of the normal subjects showed gain values that were higher during combined eye-head tracking than ocular tracking. This reflected the low gain values for torsional OKN. In the normal subjects, the gain of the visually enhanced VOR was lower in the torsional plane than in the horizontal or vertical planes, ranging from 0.19 to 0.64. Examples from one subject are shown in Fig. 7A,C,E. Note that, for all torsional testing of combined eye-head tracking, head velocity was equal to target velocity (*see* Methods).

All of the patients also showed gain values that were higher during combined eye-head tracking than ocular tracking (Fig. 7B,D,F); in some, the OKN response was hardly measurable. The gain of the visually enhanced VOR varied but was not generally lower than in the normal subjects, ranging from 0.30 to 0.70. Because the stimuli used in the torsional plane were all at approximately 0.5 Hz, it was possible to compare results from the group of subjects with the group of patients. No significant difference between the gain values of OKN, combined eye-head tracking or visually enhanced VOR could be demonstrated between the two groups.

When the torsional results were used to test the model shown in Fig. 1, the predicted combined eye-head tracking gain was within 10% of the measured value for only two subjects (S4, S5). All other subjects and all patients, with the exception of one (P14), showed greater values of combined eye-head tracking gain than predicted by the model (Fig. 5, bottom panel). Note that in some subjects and patients the OKN response was so small that a reliable estimate of gain could not be made, and the model could not then be tested.

Fixation and saccades

We did not aim to test comprehensively the fixation and saccadic behaviour of our patients and summarize only certain qualitative features. Fixation was steady in primary and in eccentric gaze in all subjects except for three (S4, S5, S7) who showed occasional small, saccadic intrusions, i.e. 'square-wave jerks' (*see* Rascol *et al.*, 1991). Two patients with Parkinson's disease (P1, P3), two with miscellaneous conditions (P12, P13) and all patients with progressive supranuclear palsy or cerebellar degeneration showed square-wave jerks. Only the four patients with cerebellar disease showed gaze-evoked nystagmus; in addition, two of them showed small-amplitude nystagmus in the primary position which was downbeating (P12) or horizontal (P10). All normal subjects showed saccades that were of normal velocity and accuracy. All patients with Parkinson's disease and cerebellar degeneration showed saccades that were of normal velocity in the horizontal and vertical planes, with the exception of one with Parkinson's disease (P1) who showed borderline slowing of upward-directed saccades. Patients with cerebellar disease showed varying degrees of saccadic dysmetria. All patients with Parkinson's disease and the patient with cortical-basal ganglionic degeneration showed some hypometria of saccades, especially vertically. All patients with progressive supranuclear palsy showed hypometria of horizontal saccades and slowing of vertical saccades. In addition, a patient with an ill-defined degenerative disease (P13) showed slow, hypometric vertical saccades.

DISCUSSION

We have shown that patients with a variety of lesions involving the brainstem and cerebellum, and certain normal subjects, may show superior tracking of an object moving

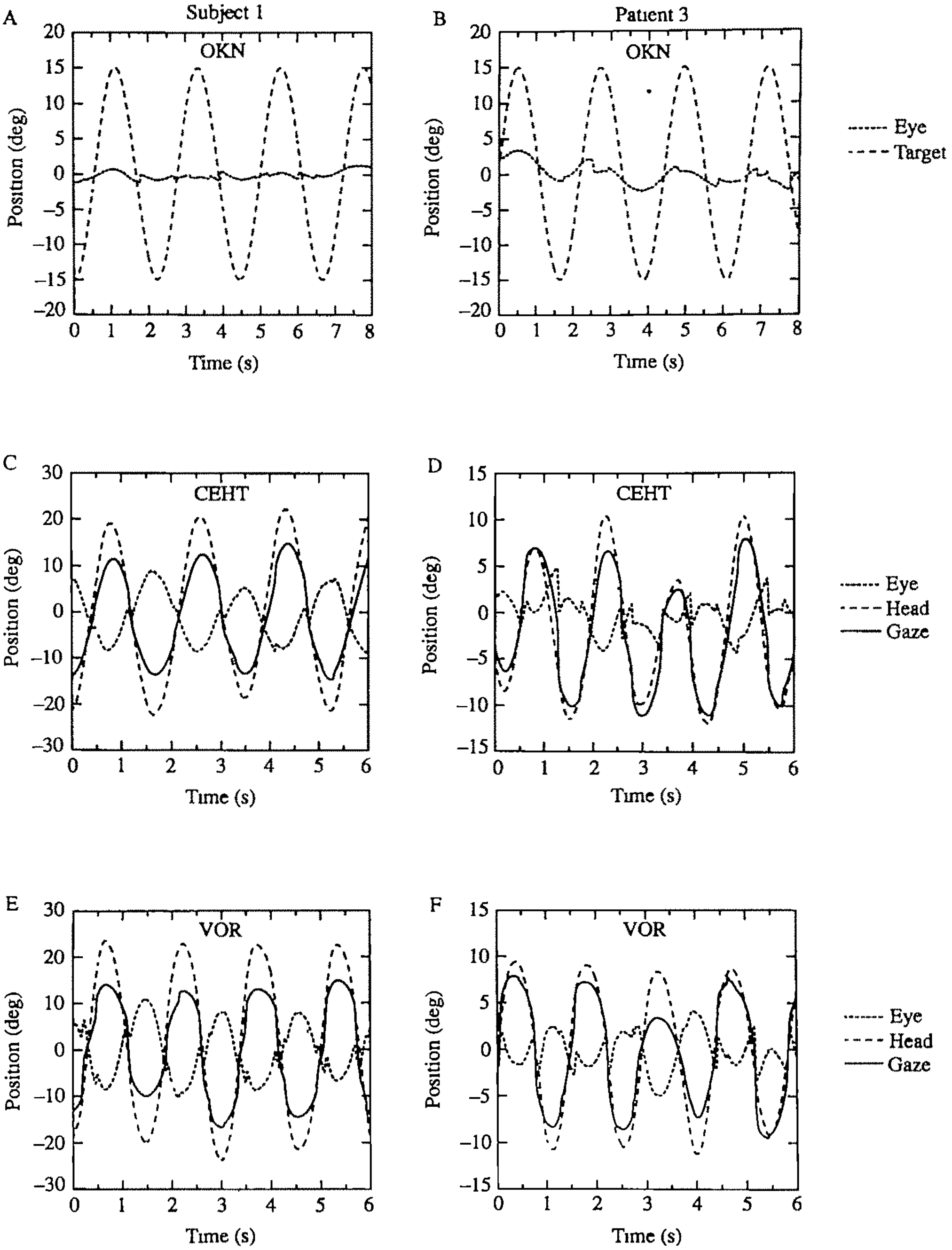

FIG. 7 A comparison of ocular tracking [optokinetic nystagmus (OKN)], combined eye-head tracking (CEHT), and the visually enhanced VOR in the torsional plane. Panels A, C and E are from S1; panels B, D and F are from P3, who has Parkinson's disease. Both normal subject and patient show weak OKN responses (this patient's was the greatest measured). During combined eye-head tracking, the torsional VOR remains partially active, and tracking gain is 0.70 for the subject and 0.64 for the patient. The visually enhanced VOR is 0.45 for the subject and 0.55 for the patient, both less than corresponding values in the horizontal and vertical planes

smoothly in the horizontal or vertical planes if they used combined eye-head tracking rather than purely ocular pursuit movements. Less commonly, ocular tracking is superior to combined eye-head tracking. In the torsional plane, combined eye-head tracking was always superior to ocular tracking (i.e. torsional OKN); this was the case in both normal subjects and in patients. Thus the results from testing in the torsional plane appeared qualitatively different from those in the horizontal and vertical planes, and are discussed separately.

Possible mechanisms for ocular tracking and combined eye-head tracking in the horizontal and vertical planes

Combined eye-head tracking was superior to ocular tracking in patients from all diagnostic groups and was also seen in our older normal subjects. This phenomenon was most striking in patients with progressive supranuclear palsy, who were unable to generate vertical saccades to compensate for their impaired ocular tracking. The pathogenesis of impaired horizontal and vertical smooth pursuit in our patients probably varied. For example, in the patients with cerebellar disease, disturbance of a descending smooth pursuit pathway that has been shown to pass through the flocculus and vermis (Pierrot-Deseilligny *et al.*, 1989; Leigh and Zee, 1991) was probably involved. The impairment of smooth pursuit in progressive supranuclear palsy and Parkinson's disease is less well accounted for (Troost and Daroff, 1977; White *et al.*, 1988), as is the well-documented deterioration that occurs in healthy elderly subjects (Zackon and Sharpe, 1987). Mild asymmetries of smooth pursuit and combined eye-head tracking (left-right or up-down) were evident in some of our subjects and patients; such asymmetries have been previously reported in normal subjects and patients with brainstem lesions (Baloh *et al.*, 1988; Ranalli and Sharpe, 1988; Pierrot-Deseilligny *et al.*, 1989). In our study, however, these asymmetries were too small to affect the values of gain calculated for each overall response.

Irrespective of the cause, it was a common finding that combined eye-head tracking was relatively preserved compared with ocular tracking, suggesting the existence of an independent mechanism or pathway from that subserving smooth pursuit. This idea is supported by studies from other laboratories that have demonstrated different properties of ocular tracking and combined eye-head tracking in normal subjects (McKinley and Peterson, 1985, Kasteel-van Linge and Maas, 1990), especially at higher stimulus frequencies. Superior performance of combined eye-head tracking over ocular tracking might be more evident at higher target accelerations, when ocular tracking tends to break down (Lisberger *et al.*, 1981); in this study, however, we used only one stimulus frequency for each individual.

In this study we set out to test a simple model, which proposes that the VOR is cancelled by an internal ocular tracking command during combined eye-head tracking (Fig. 1). The results of testing this model (Fig. 5) imply that, for most normal subjects, an internal ocular tracking signal is all that is required to cancel the VOR during combined eye-head tracking in the horizontal and vertical planes. The model also accounted for the behaviour of some patients, including one (P11) who showed ocular tracking that was superior to combined eye-head tracking, and had a hyperactive VOR. On the other hand, the model failed to account for the findings in most of our patients with brainstem and cerebellar disease, and our elderly normal subjects, whose ocular tracking was impaired.

If this simple cancellation mechanism does not account for the findings in most of our patients, what other mechanism could cause combined eye-head tracking to be superior to that predicted by the model? One possibility is that the gain of the VOR is reduced, due to the effects of mental set, during combined eye-head tracking (*see* Introduction). Thus, a prediction of the model is that, if smooth pursuit gain is low (e.g. less than 0.5), a relatively small decrease in the internal gain of the VOR would be expected to produce an appreciable increase in the gain of combined eye-head tracking. In this case, of course, the model is no longer linear but incorporates the idea of a change in parameter values (i.e. g_{vor}) according to the task (i.e combined eye-head tracking versus visually enhanced VOR). Nonetheless, there is no reason why two mechanisms (cancellation of the VOR by an internal signal and reduction of the gain of the VOR) should not both contribute during combined eye-head tracking (Lisberger, 1990; Magenes *et al.*, 1990; Cullen *et al.*, 1991). Indeed, recent studies utilizing the 'brake experiment', in which the subject's head is unexpectedly stopped during combined eye-head tracking, suggest that both mechanisms do contribute (Leigh and Huebner, 1993). If this is the case, then , in our patients, the ability to modulate the gain of the VOR during combined eye-head tracking was apparently preserved, even though ocular tracking was impaired. This may be contrasted with vertical tracking in patients with bilateral internuclear ophthalmoplegia; such patients show combined eye-head tracking that is worse than predicted, implying impaired ability to modulate their VOR gain, even though this is reduced (Ranalli and Sharpe, 1988).

It is also possible that during combined eye-head tracking the neural signal for tracking is more robust than during smooth pursuits. Thus, a 'predictor mechanism' which has been well demonstrated for smooth pursuit (Bahill and McDonald, 1983; Becker and Fuchs, 1985; Barnes and Asselman, 1991), might be enhanced during combined eye-head tracking so that gaze follows the target more accurately. Certain patients, however, appeared to maintain certain predictable characteristics of smooth pursuit despite a low overall tracking gain; for example in Fig. 3B, note how the parkinsonian patient P2 anticipates the turn-around in target direction, even though tracking gain is low. This patient and P3, who also had Parkinson's disease, sometimes used a strategy of anticipatory saccades to track the target and in these two patients this may have reduced tracking gain during smooth pursuit. In other patients, however, such a strategy was not apparent, and low tracking gain was due to low-velocity smooth eye movements.

Finally, it should be noted that, in patients with a low VOR gain, combined eye-head tracking gain will be improved with larger velocity head movements; such behaviour is predicted by the model of Fig. 1. Thus, for example, patients with internuclear ophthalmoplegia, who show a hypoactive vertical VOR, have been shown to use a strategy of large head movements to increase the gain of their vertical combined eye-head tracking (Ranalli and Sharpe, 1988). Only our cerebellar patients tended to generate head velocities that exceeded target velocity, and they also tended to have reduced VOR gain values. However, whether this behaviour was adaptive or simply due to ataxia of head movements was unclear.

Possible mechanisms for ocular tracking and combined eye-head tracking in the torsional plane

Neither the data for normal subjects nor from patients in the torsional plane could be accounted for by the model in Fig. 1. Furthermore, when normal subjects and patients were compared as groups, the gain of ocular tracking (torsional optokinetic response), combined eye-head tracking and visually enhanced VOR were similar. This was quite different from results in the horizontal and vertical planes, where most patients showed combined eye-head tracking that was superior to ocular tracking, and most subjects showed ocular tracking that was similar to combined eye-head tracking. No matter how severely ocular tracking was affected in the horizontal or vertical planes, the torsional responses were no different from control subjects.

It might be argued that combined eye-head tracking in roll is a special case, in which the image of a small object never moves off the foveal region (Leigh *et al.*, 1989; Seidman and Leigh, 1989). Nonetheless, there must be some mechanism to reduce the internal gain of the VOR while subjects attempt to view a visual display that moves with their heads in the roll plane (Leigh *et al.*, 1989), and this mechanism can neither be torsional smooth pursuit (a meaningless concept, *see* Robinson, 1982) nor the torsional optokinetic system, which is feeble in both normal subjects and patients (Collewijn *et al.*, 1985; Morrow and Sharpe, 1989). Rather, the VOR itself must either be suppressed or cancelled by a signal that is neither smooth pursuit or OKN; possible candidates include a self-cancellation mechanism (Tomlinson and Robinson, 1981; Cullen *et al.*, 1991), an intended head movement command (Robinson, 1982) or the effects of prediction (Seidman *et al.*, 1992). Whatever the mechanism, disease of the brainstem and cerebellum that impairs horizontal and vertical smooth pursuit and combined eye-head tracking does not necessarily produce similar deficits in the torsional plane.

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A QUANTITATIVE STUDY OF EYE AND HEAD MOVEMENTS DURING SMOOTH PURSUIT IN PATIENTS WITH CEREBELLAR DISEASE

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SUMMARY

Eye and head movements were analysed during smooth pursuit in 16 patients with various forms of cerebellar disease. Smooth pursuit gain was reduced across all frequencies and velocities of target motion for the patient group as a whole, during both sinusoidal and pseudo-random target motion. The graded breakdown in the pursuit response, as pseudo-random target motion became less predictable, was of a similar magnitude in patients and controls, implying that the predictive pursuit mechanisms were intact in these patients. During head-free pursuit, when vestibulo-ocular reflex (VOR) suppression was necessary, performance was not significantly different from that observed during head-fixed pursuit in the patient group. This finding is similar to that noted in control subjects, and is consistent with the observation that the VOR gains associated with head movements in darkness were similar in the patient and control groups. The deficits in pursuit and VOR suppression in patients with cerebellar disease therefore represent a decrease in gain in the closed-loop visual feedback pathways with apparent sparing of the predictive pathways.

INTRODUCTION

The critical role of the cerebellum in smooth eye movement control has been well established in numerous animal (Westheimer and Blair, 1974; Zee *et al.*, 1981) and human studies (von Noorden and Preziosi, 1966; Baloh *et al.*, 1975, 1986; Zee *et al.*, 1976; Dichgans *et al.*, 1978; Monday *et al.*, 1978; Avanzini *et al.*, 1979; Estanol *et al.*, 1979; Wennmo *et al.*, 1983; Ell *et al.*, 1984; Furman *et al.*, 1986; Yamamoto *et al.*, 1988; Pierrot-Deseilligny *et al.*, 1990). Cerebellar lesions and degenerations usually cause disruption of smooth tracking by reducing maximal smooth eye velocity, resulting in the characteristic broken eye displacement trace consisting of low velocity slow phases punctuated by catch-up saccades. These features have been a consistent finding in all of the above studies where pursuit performance has been assessed using predictable target motion.

In constructing control systems models of the smooth pursuit system, it has generally been assumed that at least two feedback loops are responsible for optimal tracking performance (Dallos and Jones, 1963; Robinson, 1965; Young, 1971; Yasui and Young, 1984; Becker and Fuchs, 1985; Barnes and Asselman, 1991). It has been postulated that a closed loop, visual feedback pathway corrects eye velocity according to retinal velocity error, but such a simple system cannot explain how it is possible to maintain

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steady state pursuit of a moving target with the low levels of phase error observed experimentally in the face of the established delays in the visual pathways. An additional predictive pathway is needed to enable the oculomotor system to produce eye movements which attempt to match future estimates of target motion based on information derived from the previous target trajectory. These predictive strategies are able to eliminate the inherent phase lags resulting from time delays in the visual and oculomotor pathways, and would therefore be expected to make an important contribution to pursuit performance, particularly as target frequency increases.

Cerebellar disease can result in the most severe deficits of smooth pursuit, but predictive behaviour in the pursuit system has not been specifically addressed in patients with cerebellar disease. Recordings from the primate cerebellar flocculus indicate that a predictive pattern of firing behaviour can be observed in neurons which encode eye velocity (Lisberger and Fuchs, 1978; Noda, 1986), but the exact source of this activity is unclear. It might be anticipated that, if the predictive mechanisms were disturbed by cerebellar lesions, performance would be relatively preserved at low target frequencies, as it is in some patients with mild cerebellar disease (Zee *et al.*, 1976). However, because it is difficult to examine prediction in isolation, it has not been conclusively demonstrated that the predictive mechanisms are functioning normally in these patients. Phase differences between target and eye velocity give some indication of predictive behaviour, but a number of problems arise in the interpretation of phase changes in patients with low gain pursuit. A reduction in gain of itself will cause an increase in the degree of phase lag, thereby masking any predictive effects which might be occurring, and documentation of phase changes becomes less accurate when gain falls, particularly at higher target frequencies.

Using an alternative approach to this problem, it has been demonstrated that pseudo-random stimuli can be used with great effect to study the breakdown in the predictive behaviour of the smooth pursuit response (Barnes *et al.*, 1987; Barnes and Ruddock, 1989). The predictability of a pseudo-random stimulus composed of the sum of two or more sinusoids is determined not by the number of frequency components contained within the stimulus, but by the frequency of the highest frequency component. Low frequency pseudo-random stimuli are very predictable but, if the stimulus contains a frequency component which is above a critical level of 0.4 Hz, the target motion becomes less predictable and a breakdown in the gains of all the lower frequency components occurs (Barnes *et al.*, 1987). When the velocity of the high frequency component is increased with respect to the velocity of the other components, further breakdown occurs. We have therefore performed a study of smooth pursuit in patients with various forms of cerebellar disease using pseudo-random and sinusoidal stimuli to investigate predictive smooth pursuit function and to quantify the frequency and velocity characteristics of the pursuit deficits in these patients.

When both head and eye movements are used to track smooth target motion, accurate gaze control depends on adequate suppression of the vestibulo-ocular reflex (VOR) which, if unopposed, would produce eye movements of opposite polarity to head movement. The ability to suppress the VOR generated by either rotational or caloric stimuli is reduced in patients with cerebellar disease and is generally considered to correlate directly with the smooth pursuit deficit, implying a common pathway involving the cerebellar connections for both functions (Zee *et al.*, 1976; Dichgans *et al.*, 1978; Henriksson *et al.*, 1984; Baloh *et al.*, 1986). Therefore, we have also investigated head-free pursuit and compared the measures of smooth combined eye and head, or gaze velocity, with those obtained under head-fixed conditions during pseudo-random target motion tracking. Because the underlying level of VOR gain will be expected to influence head-free pursuit performance, an estimate of the VOR gain at the frequencies used in the pseudo-random stimulus was also obtained in each of the subjects, using various real and imaginary target paradigms during active head movements and passive whole body rotation.

METHODS

Subject selection

A total of 16 patients with cerebellar disease (mean age 44.8 yrs, range 23–66 yrs) resulting from a number of different pathological processes were studied (Table 1), though not all patients did every test. Patients had either pure cerebellar involvement in the form of hereditary or sporadic cerebellar degeneration with no clinical or investigative evidence of other neurological involvement, or cerebellar signs in combination with other central neurological features.

Patients in the latter group, particularly those with multiple sclerosis, were chosen because the major clinical features were consistent with dysfunction in cerebellar pathways, and all had clinical evidence of bilateral involvement. The patients with multiple sclerosis were examined to ensure that there were no other signs of oculomotor involvement, such as ophthalmoplegia or saccadic slowing, which might have influenced the eye movement recordings. In the one patient with a mild internuclear ophthalmoplegia, recordings were taken from the unaffected eye.

Patients with dementia or uncontrolled head tremor were excluded from the study. A similar number of naive, age-matched controls performed each experiment (mean age 45.8 yrs, range 23–69 yrs). All subjects participated with informed consent and the experiments were approved by the local ethics committee.

Apparatus

The subjects were seated in the centre of a darkened room in front of a semicircular screen of radius 1.5 m. Eye movements were recorded using an infrared limbus reflection technique (Iris 6500 system, Skalar Medical) with a resolution of 10 min of arc and a linear range of at least ±20 degrees. The eye

TABLE 1 SUMMARY OF PATIENTS

Case no	*Age/sex*	*Diagnosis*	*Other oculomotor signs*
1	43/F	Cerebellar degeneration	Gaze evoked nystagmus
2	42/F	Cerebellar degeneration	Gaze evoked nystagmus
3	62/F	Cerebellar degeneration	Gaze evoked nystagmus
4	56/F	Cerebellar degeneration	Gaze evoked nystagmus
5	65/F	Cerebellar degeneration	Gaze evoked nystagmus, square wave jerks
6	52/M	Cerebellar degeneration	Gaze evoked nystagmus, saccadic dysmetria
7	58/M	Spinocerebellar degeneration	Gaze evoked nystagmus
8	28/M	Spinocerebellar degeneration	Gaze evoked nystagmus, slow saccades
9	23/F	Spinocerebellar degeneration	Square wave jerks, saccadic dysmetria
10	26/F	Multiple sclerosis	Gaze evoked nystagmus, R. internuclear ophthalmoplegia
11	39/F	Multiple sclerosis	Gaze evoked nystagmus
12	53/F	Multiple sclerosis	Gaze evoked nystagmus
13	39/F	Friedreich's ataxia	Square wave jerks, saccadic dysmetria
14	33/M	Friedreich's ataxia	Gaze evoked nystagmus, square wave jerks
15	66/F	Multiple system atrophy	Gaze evoked nystagmus, hypometric saccades
16	31/M	Hereditary spastic paraparesis with cerebellar features	Gaze evoked nystagmus

movement recorders were mounted on a helmet assembly which was attached firmly to the subject's head. A single turn potentiometer, attached to the top of the helmet via a flexible assembly, was used to record head displacement. During experiments performed under head-fixed conditions, a head clamp and chin rest were used to stabilize the head. The target consisted of a small white cross within a circle, the diameter of which subtended 70 min of arc at the eye, and its motion was controlled by a motor-driven mirror situated above the subject's head. A motorized turntable (Toennies, 200 Nm) was used to assess vestibular function during sinusoidal oscillation. Eye movement calibrations were performed prior to each subtest.

Experimental design

Experiment (i). Pursuit of predictable sinusoidal target motion was investigated under head-fixed conditions at frequencies of 0.20, 0.40, 0.82, 1.20 and 1.56 Hz. For each set of stimuli the peak amplitude was set at ±5, 10 or 15 degrees, thus producing peak stimulus velocities between 6 and 147 degrees/s. A total of 15 patients performed this test.

Experiment (ii). Head-fixed performance was examined during pursuit of a pseudo-random stimulus composed of the sum of three or four sinusoids of frequency 0.11, 0.24, 0.37 and 1.56 Hz (Fig. 1). The velocity of the three lowest frequency components remained constant at 8 degrees/s, while the velocity of the 1.56 Hz component was varied as a ratio (velocity ratio, VR) of the lower frequency velocities between 0 and 2, the 1.56 Hz component therefore being absent when the velocity ratio was zero. A total of 14 patients performed this test.

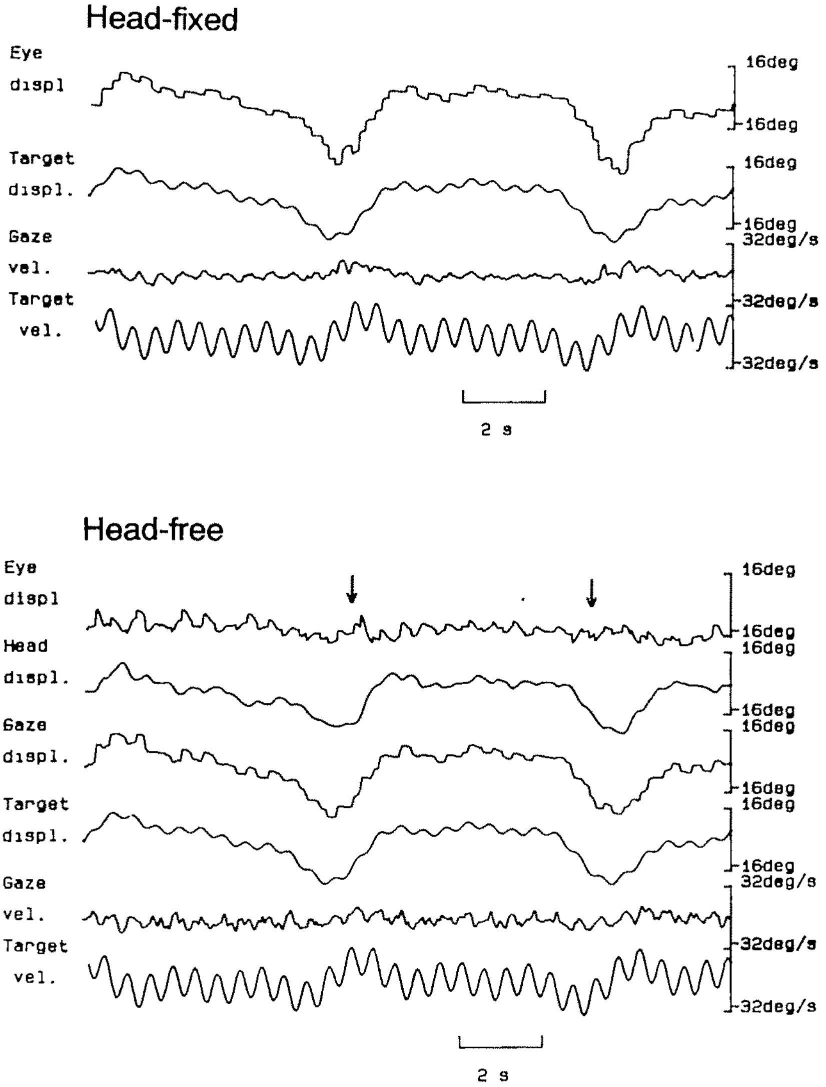
Experiment (iii). A direct comparison of head-fixed and head-free pursuit was performed in 10 patients. The pursuit stimuli were the same pseudo-random waveforms used in experiment (ii). All conditions were presented in random order. For the head-free conditions the subject was asked to use natural, combined eye and head movements to track the target (Fig. 1).

Experiment (iv). The vestibular response was recorded during active head movements and passive whole body turntable rotation. Each of the three lowest frequencies used in the pseudo-random stimulus (0.11, 0.24, 0.37 Hz) was presented as a sinusoidal waveform with a peak velocity of 16 degrees/s to approximate the root mean square velocity of the pseudo-random waveform. Using combined eye and head movements, subjects were initially instructed to follow the target in time with a stationary, sinusoidally modulated tone located above the subject's head. Subsequently, the target was extinguished and the subject was asked to follow an imaginary target in complete darkness, moving his head in time with the tone (active VOR). We have shown previously that this paradigm does not result in any significant degree of VOR suppression in normal subjects (Waterston and Barnes, 1991). Head movements were monitored on an oscilloscope by an observer and the subject was prompted if either the timing or the amplitude of head movement was inappropriate. The target frequencies were presented in randomized fashion, but the imaginary target conditions always followed the real target condition. Because some patients had difficulties performing the test, results from eight patients only were used for analysis.

The sequence of real and imaginary target tracking was then repeated using a stationary fixation target (earth-fixed target, EFT and imaginary earth-fixed target, IEFT); the results were analysed from six patients. Vestibular responses during sinusoidal whole-body rotation (passive VOR) were recorded in 11 patients at the same frequencies and velocities, while subjects performed mental arithmetic to maintain alertness. On the basis of these results, subjects who performed the head-free task were divided arbitrarily into a low VOR gain (gain at two or more frequencies <0.5) and a high VOR gain group (remaining subjects). It is important to note that these groups did not necessarily represent patients with abnormal VOR gains.

Analysis

All experiments were controlled and analysed off-line by computer (Hewlett-Packard 360CH) using techniques described previously (Barnes *et al.*, 1987). Gaze displacement was obtained by summing eye and head displacement, and gaze velocity was calculated by differentiating gaze displacement. A computer graphics procedure was used to remove the saccadic components from the gaze velocity trace (Barnes, 1982). The resultant measure of slow-phase eye velocity (or gaze velocity during head-free experiments) was then correlated with target velocity to produce eye (or gaze) velocity gain and phase. All subsequent references to eye or gaze velocity gain refer to slow-phase velocity gain. Slow-phase eye velocity was correlated with either head or turntable velocity to produce VOR gain. Statistical significance was assessed by analysis of variance.



Fɪɢ 1. Traces of eye, head, gaze and target displacement, and eye and gaze velocity during head-fixed and head-free pursuit of pseudo-random target motion The stimulus contained 0.11, 0.24, 0.37 (peak velocity 8 degrees/s) and 1.56 Hz sinusoids (peak velocity 16 degrees/s, i.e. velocity ratio of 2). The fast phases have been removed from the eye and gaze velocity traces Note the similarity between the eye and gaze displacement traces during head-fixed and head-free pursuit, respectively. Arrows mark clear examples of unsuppressed vestibular activity during head-free pursuit.

RESULTS

Experiment (i): sinusoidal pursuit

There were no qualitative differences between the pursuit patterns of patients with and without extra-cerebellar involvement. Eye velocity gain (Fig. 2) was significantly

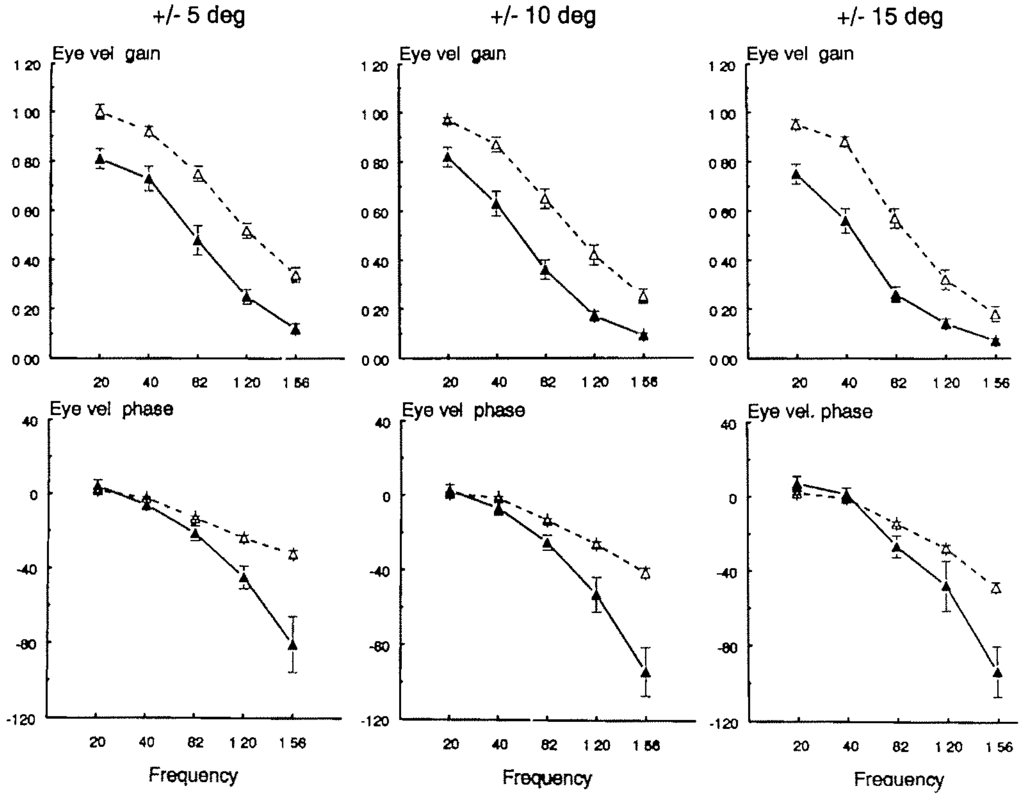


FIG. 2. (Slow-phase) eye velocity gain and phase for patients (▲) and controls (Δ) during pursuit of sinusoidal target motion at ±5, 10, 15 degrees amplitudes Mean ± 1 SE (n = 15)

reduced in the patient group for all frequencies and amplitudes of target motion ($P < 0.001$). Although the decrease in gain for both groups was more marked with increasing frequency, there was also a significant decrease in gain with increase in velocity, particularly when target velocity exceeded 25 degrees/s at frequencies of 0.4 Hz and above ($P < 0.05$), e.g. at 0.4 Hz the gain decreased from 0.73 when the peak velocity was 13 degrees/s (amp. of ±5 degrees) to 0.56 when peak velocity was 38 degrees/s (amp. of ±15 degrees). For the control group the corresponding gains were 0.92 and 0.88. At the lowest frequency there was a small phase advance for eye velocity in both groups, but an increasing phase lag was observed as frequency increased (Fig. 2), which was significantly greater in the patient group at frequencies above 0.4 Hz ($P < 0.001$). Overall eye displacement gain (Fig. 3) which included saccadic components, was similar for patient and control groups up to 0.4 Hz, but for patients was significantly reduced at higher frequencies of target motion ($P < 0.005$). A number of mildly affected patients had relatively preserved eye velocity gains at low target frequencies, whereas the more severely affected patients had reduced gains across all frequencies.

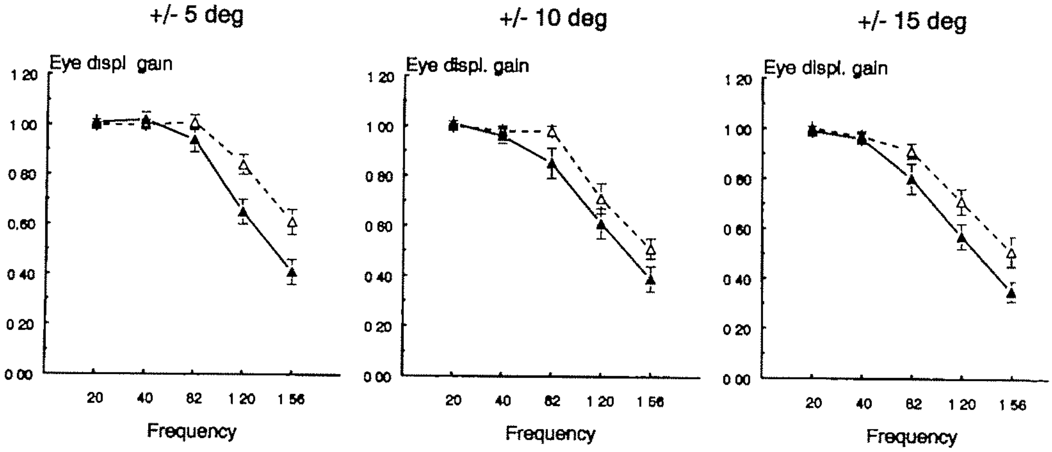


FIG 3 Eye displacement gain for patients (▲) and controls (△) during pursuit of sinusoidal target motion. Mean ±1 SE (n = 15).

Experiment (ii): pseudo-random target motion

When the pseudo-random stimulus contained only the three lowest frequency components (VR = 0), mean eye velocity gain in the control group was always above 0.9 (mean 0.95). In contrast, the patient group had gains which were significantly reduced (mean 0.74, $P < 0.001$). As the stimulus was made less predictable, initially by adding in the high frequency (1.56 Hz) component to the stimulus, and then by increasing its velocity with respect to the lower frequency velocities, there was a progressive breakdown in the eye velocity gains at the three lowest frequencies for both groups (Fig. 4A), a feature which has been noted previously in studies of normal subjects (Barnes *et al.*, 1987; Barnes and Ruddock, 1989) The breakdown in the low frequency gains with increasing velocity ratio was of a similar magnitude in the patient and control groups, except that eye velocity gain was always significantly lower overall in the patient group ($P < 0.001$). The pattern of breakdown was also similar in the patients with and without extra-cerebellar involvement.

The patterns of eye velocity phase were almost identical in the two groups (Fig. 4B). In common with previous observations, as the velocity ratio was increased there was an increasing phase lead at the lower frequency, and a progressive phase lag at all other frequencies except at the highest frequency where the phase lag decreased (Barnes *et al.*, 1987; Barnes and Ruddock, 1989).

Experiment (iii): comparison of head-fixed and head-free pursuit

During head-free pursuit there was no significant difference in head displacement gain between patients and controls. Mean head displacement gain for the patient group was 0.67 (range 0.57–0.87) at the three lowest frequencies but fell to 0.41 (range 0.25–0.51) at the highest frequency. A progressive phase lag for head displacement was seen with increasing frequency and, to a lesser extent, with increasing velocity ratio. When the direct comparison of head-fixed and head-free pursuit was made, no

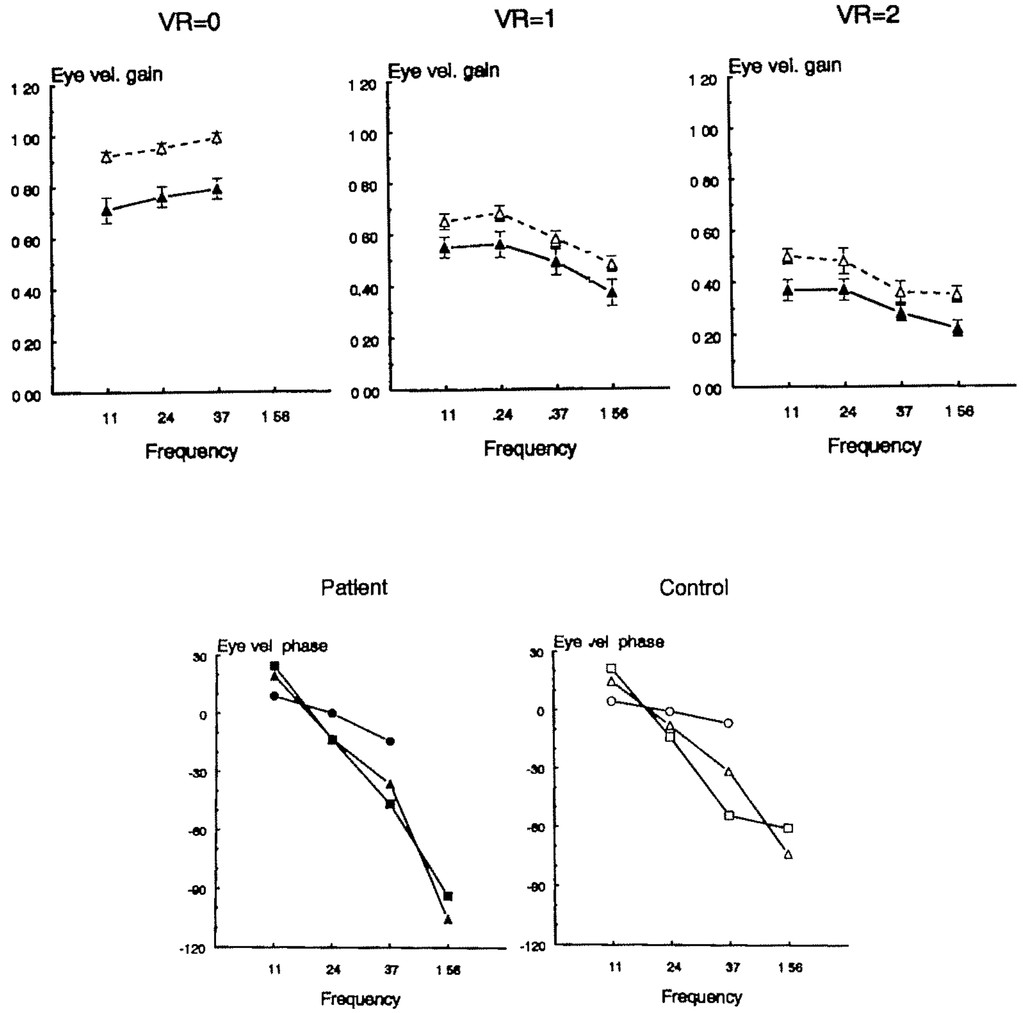


FIG. 4. Eye velocity gain for patients (▲) and controls (△) (*top*), and phase (*bottom*) during pursuit of a pseudo-random stimulus containing the sum of three or four sinusoids (of frequency 0.11, 0.24, 0.37, 1.56 Hz). The peak velocity of the three lowest frequency sinusoids was always 8 degrees/s, while the velocity of the 1.56 Hz sinusoid was varied as a ratio (velocity ratio VR) of the lower frequency velocity between 0 and 2. VR = 0, circles; VR = 1, triangles; VR = 2, squares For eye velocity gain, each graph represents a separate stimulus. Mean ± 1 SE (n = 14).

significant differences were found for gaze velocity gain at any velocity ratio or frequency (Fig. 5), and almost identical patterns of phase change were seen under both head conditions for patients and controls, similar to those described in the previous experiment.

These results were analysed separately for the high VOR gain (mean gain 0.77 for all frequencies, n = 7) and low VOR gain (mean gain 0.46, n = 3) groups, as defined in the Methods section. However, no significant differences were found between head-fixed and head-free performance in either group, although the overall levels of

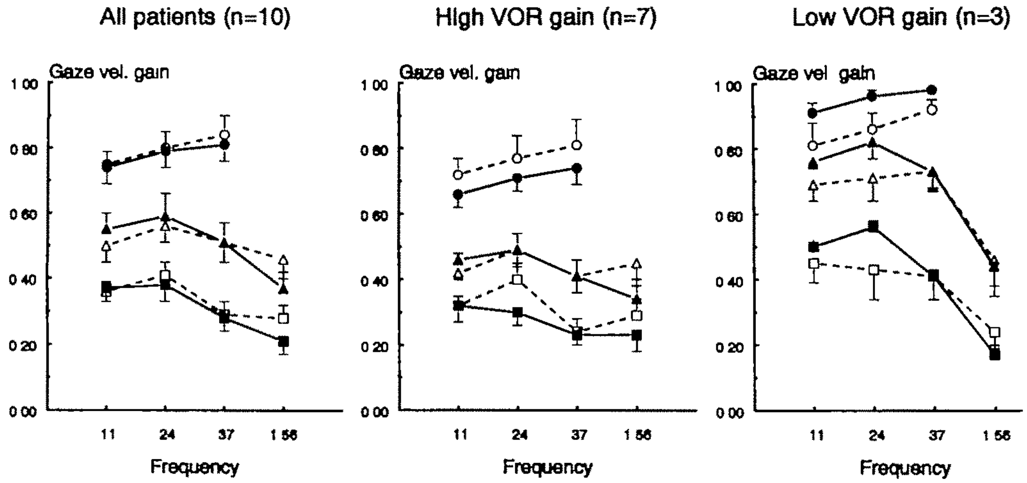


FIG. 5 Comparison of gaze velocity gain for head-fixed and head-free pursuit of pseudo-random target motion in all patients (n = 10) (*left*), those with high VOR gain (n. = 7) (*middle*) and low VOR gain (n = 3) (*right*). *See* Methods for definition of subgroups. Mean ± 1 SE. Closed symbols: fixed (VR = 0, circles; VR = 1, triangles; VR = 2, squares); open symbols: free.

gaze velocity gain were higher in the low VOR gain group. The gain levels in the low VOR gain group were similar to the control group means at the three lowest frequencies but, as in the sinusoidal pursuit experiments, these mildly affected patients had a fall-off in gain at the highest frequency (Fig. 5).

Experiment (iv): VOR gain

The VOR gains observed during whole body turntable rotation in the dark were higher for the patient group than for the controls (Fig. 6A), but this effect was significant only at 0.24 Hz (0.80 versus 0.53, $P < 0.05$). The overall variance in the patient group was higher, reflecting the fact that a number of patients had either very low or rather high VOR gains (range of standard deviation for the patient group was 0.24–0.35 for the three frequencies, versus 0.10–0.18 for controls). The three patients with the lowest VOR gains included one patient with Friedreich's ataxia and two with spinocerebellar degeneration, although only one of the spinocerebellar patients had gains which fell outside two standard deviations of the control group means. When subjects performed active head movements in the dark at similar frequencies, the VOR gains were similar for the two groups (average of 0.64 for patients and 0.68 for controls). In control subjects there was an increase in VOR gain during active as compared with passive head movements. In contrast, the gains in the patient group were less during active head movements (Fig. 6A), although the difference between active and passive VOR gains was only significant for the control group ($P < 0.01$).

Control subjects were able to fixate an earth-fixed target during active head movements with a gain close to unity (mean 0.98, Fig. 6B). The patients were also able to perform this task by enhancing the baseline VOR gain (i.e. that recorded in the dark), but the

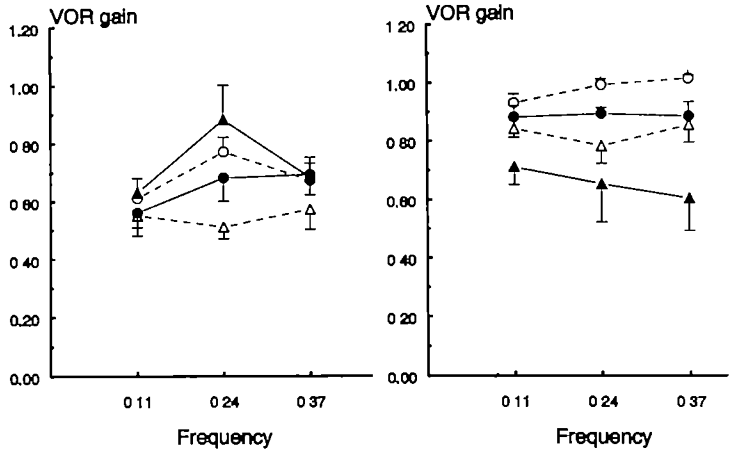


FIG. 6. *Left*, comparison of slow-phase eye velocity gain of VOR produced by whole-body turntable rotation (passive VOR; triangles) and active head movements (active VOR; circles) in the dark for cerebellar patients (closed symbols) and controls (open symbols). Mean ± 1 SE (n = 8). *Right*, comparison of VOR observed during active head movements under conditions of real earth-fixed target fixation (EFT; circles), and imagined earth-fixed target fixation (IEFT; triangles) in the dark for cerebellar patients (closed symbols) and controls (open symbols). Mean ± 1 SE (n = 6).

gains were still significantly less than normal (mean 0.88, $P < 0.001$). The control subjects were also able to elevate VOR gain by imagining an earth-fixed target in the dark, although the levels of gain were less than those seen in the light (mean 0.82). In contrast, the cerebellar patients were unable to enhance their VOR gains in the dark using imaginary targets (mean 0.65 for IEFT condition versus 0.64 for VOR condition), even though they clearly understood the instruction (Fig. 6A,B).

DISCUSSION

The abnormalities of smooth pursuit described in these patients are similar to those reported previously by other authors. The patient group as a whole demonstrated smooth pursuit deficits which were present across all frequencies and velocities of target motion, irrespective of the predictability of the stimulus waveform. Performance was not greatly different under head-fixed and head-free conditions for both patients and controls, this finding being consistent with the similar levels of VOR gain observed during active head movements in both subject groups. There were no significant qualitative differences in the pursuit deficits of those patients with relatively pure cerebellar disease and those with various forms of extra-cerebellar involvement. For the purposes of discussion these patients will therefore be discussed as a single group.

The basis of the smooth pursuit deficit in cerebellar disease

On the evidence of ablation and single-unit recording studies in animals, it has been concluded that the cerebellar flocculus is intimately involved in smooth eye movement control (Miles and Fuller, 1975; Lisberger and Fuchs, 1978; Miles *et al.*, 1980; Zee *et al.*, 1981). However, the contribution from other cerebellar structures such as the vermis is also important (Suzuki *et al.*, 1981; Furman *et al.*, 1986; Pierrot-Deseilligny *et al.*, 1990), as demonstrated by the finding that smooth pursuit is not completely abolished by flocculectomy (Zee *et al.*, 1981). In view of the similar visual feedback mechanisms underlying pursuit and VOR suppression (Barnes *et al.*, 1978), it is also not surprising that the flocculus has been shown to be essential for suppression of the VOR (Takemori and Cohen, 1974).

The patient group had reduced smooth eye velocity gains across all target frequencies and velocities, though some of the less severely affected patients had relative preservation of gain at low frequencies during both sinusoidal and pseudo-random pursuit, as documented previously in patients with cerebellar degeneration (Zee *et al.*, 1976). The decrease in gain occurred with both an increase in stimulus frequency and peak velocity, and at the higher frequencies there was a greater phase lag in the patient group. Overall gaze displacement was not significantly different from controls up to and including 0.4 Hz, indicating that the saccadic system was functioning well to make up the difference between slow-phase eye velocity and target velocity at these frequencies, but at the higher frequencies displacement gain fell significantly. On the basis of the minimal phase differences at low frequencies that we have observed, it seems likely that prediction is relatively intact at these frequencies, but it is difficult to be certain about predictive behaviour at the higher frequencies where increasing phase lags make interpretation difficult.

For this reason, the use of pseudo-random stimuli offers another means of examining the predictive mechanisms more closely. On the basis of the results from previous studies, the breakdown in the response observed during pursuit of pseudo-random target motion indicates that the predictive mechanisms are probably functioning normally at the frequencies tested. It has been demonstrated that if all the frequencies in the waveform are less than 0.4 Hz, the target motion is very predictable and the eye velocity gains for each frequency component approximate the gains obtained during pursuit of single sinusoids of the same frequency. However, as the stimulus is made less predictable by adding the high frequency component to the pseudo-random waveform and increasing its velocity with respect to the other frequency components, a progressive breakdown in the gains at the lower frequencies is observed, while the gain at the highest frequency approximates the gain obtained to a single sinusoid of the same frequency. These changes have been attributed to the existence of a predictive velocity estimation mechanism which preferentially enhances pursuit gain at the highest frequency. Because this system is only able to operate over a relatively narrow frequency band at frequencies above 0.4 Hz, gain consequently falls at the lower frequencies (Barnes and Ruddock, 1989). Further increases in the frequency of the highest frequency component above a level of 1.6 Hz do not result in any further gain breakdown (Barnes *et al.*, 1987). These baseline gain levels at the lower frequencies are thought to reflect the performance of the closed loop, visual feedback pathways in relative isolation. Therefore the differences in gain, for each of the low frequency components between the plots for velocity ratios of 0 and 2, probably represent the contribution made by the predictive mechanisms. Although the gains in the cerebellar group were generally lower overall, this most likely reflects a reduced level of gain in the visual feedback pathways, as the difference in gain between velocity ratios was similar in both groups. These graded responses dependent on the velocity ratio of the stimulus were present in all patients irrespective of the severity of the pursuit deficit. Perhaps even more striking was the similarity of the phase changes in both groups. The decreasing phase lag at 1.56 Hz which occurred as velocity ratio increased has also been attributed to the predictive pathways which attempt to preferentially enhance performance at the highest frequency (Barnes *et al.*, 1987; Barnes and Ruddock, 1989). The evidence therefore suggests that prediction is still possible in patients with cerebellar disease, even though it has been inferred from some neurophysiological experiments that the cerebellum may play an important role in predictive behaviour (Lisberger and Fuchs, 1978; Noda, 1986).

It is interesting to note that the dose-related oculomotor effects of alcohol, such as smooth pursuit impairment (Wilkinson *et al.*, 1974; Baloh *et al.*, 1979*b*) and gaze evoked nystagmus (Goding and Dobie, 1986), are similar to those produced by cerebellar disease, and it has been demonstrated previously that alcohol appears to reduce the gain of the visual feedback pathways responsible for pursuit and VOR suppression, without any apparent effect on prediction (Barnes *et al.*, 1985, 1988), in a similar manner to that observed in our patients with cerebellar disease.

Head-free pursuit

The ability to suppress the VOR during head-free pursuit will have a significant influence on gaze performance, since any resultant vestibular eye movement will be counter-productive to the pursuit task. Abnormalities of VOR gain have been reported in patients with cerebellar disease; in most studies the VOR gain has been shown to be either normal or increased in patients with relatively pure cerebellar pathology (Baloh *et al.*, 1975, 1979, 1986; Zee *et al.*, 1976; Wennmo *et al.*, 1983; Henriksson *et al.*, 1984; Furman *et al.*, 1986; Thurston *et al.*, 1987), but when extra-cerebellar pathways are involved, such as occurs in Friedreich's ataxia or brainstem lesions, VOR gain may be reduced (Baloh *et al.*, 1975; Monday *et al.*, 1978; Wennmo *et al.*, 1983; Ell *et al.*, 1984). Impaired VOR suppression and abnormally high VOR gain are two possible causes for compromised head-free pursuit performance in patients with cerebellar disease.

When the patients used combined eye and head movements to track the target it was evident that many of them were unable to suppress the VOR adequately. This was quite obviously seen as an increase in vestibular eye movement on the eye displacement traces during head-free pursuit of the pseudo-random stimulus (Fig. 1). Despite this, no patient was reluctant to use head movements to pursue the target when instructed to do so. In fact, during head-free pursuit of single sinusoids in experiment (iv), six out of eight patients had head displacement gains greater than unity at one or more frequencies, indicating that they may have been using an increase in head movement to overcome the suppressed VOR, as has been documented previously in studies of vertical smooth pursuit in patients with internuclear ophthalmoplegia (Ranalli and Sharpe, 1988). However, this finding was also seen in three of the normal controls during sinusoidal pursuit, and mean head displacement gains in the patient group were not significantly different during either sinusoidal or pseudo-random head-free pursuit, so it is difficult to be certain about the significance of these findings.

When head-free and head-fixed pursuit were compared in the patients, no significant differences in gaze velocity gain were seen. Similar findings have also been well documented in previous studies of normal subjects under identical conditions (Waterston and Barnes, 1991). In other words, the advantage of the head movement in terms of any possible increase in gaze velocity gain, was negated by the unsuppressed vestibular activity produced as a result of the head movement. This is not surprising, since any decrease in visual feedback gain is likely to affect both pursuit and VOR suppression in a similar fashion (Barnes *et al.*, 1978). In some patients the similarity of the eye and gaze displacement traces for the corresponding head-fixed and head-free pursuit conditions was striking (Fig. 1). In patients with high VOR gains it might be predicted that head-free pursuit performance would be correspondingly impaired when compared with head-fixed pursuit, as has been demonstrated in a patient with cerebellar degeneration (Thurston *et al.*, 1987). None of our patients had VOR gains as high as that recorded in the latter case (1.9 at 1 Hz), but even so, when the patient group was separated arbitrarily into those with low and high VOR gains, no significant differences were found between head-free and head-fixed pursuits in either group.

VOR gain during active head movements

We have previously demonstrated that the VOR is probably not switched off, or subject to parametric gain changes, during head-free pursuit in normal subjects (Waterston and Barnes, 1991). One important implication of this finding is that gaze control will be protected from sudden head perturbations during head-free pursuit by the action of the VOR, a phenomenon which has been supported by experimental findings in monkeys (Lanman *et al.*, 1978). In an attempt to predict the expected head-free pursuit performance on the basis of the actual head-fixed pursuit and VOR gains, it was calculated that the effective VOR gain was around 0.9 during head-free pursuit. These measures of gain were found to approximate those obtained when subjects imagined an earth-fixed target while making active head movements in darkness (Waterston and Barnes, 1991). It is well known that normal subjects can significantly alter the level of VOR gain in darkness by using imaginary fixation instructions (Barr *et al.*, 1976). Therefore it was of interest that, in the patients in whom this was performed during active head movements, there was no significant increase in gain. Overall eye displacement was also unchanged in most patients implying that they were also unable to carry out the task using saccadic eye movements. Even though many of these patients often had severe pursuit deficits, most were able to increase the gain of the VOR in the light by fixating an earth-fixed target during active head movements, although the levels of gain achieved (mean 0.82) did not quite reach those found in normals (0.88).

The rather higher measures of VOR gain seen during fixation of an imaginary EFT in normal subjects have also been observed during the first 150–180 ms of transient rotations in the light or dark in normal subjects, no matter which fixation instruction was given (Gauthier and Vercher, 1990), implying that the lower estimates obtained during more prolonged sinusoidal rotation in darkness perhaps reflect ‘some default performance of a much larger gaze-control system, functioning poorly in the absence of complete information’ (Collewijn, 1989). We therefore contend that the level of VOR gain observed during active or passive head movements in darkness is probably an underestimate of the vestibular signal produced during head-free pursuit. Because the actual level of gain in the latter condition is probably not greatly different from unity, the head movement contribution during combined eye head tracking will be effectively nulled by the vestibular signal produced as a result of the head movement.

We have observed that the increase in VOR gain in patients with cerebellar disease is more marked in those patients with the more severe pursuit deficits (Fig. 5), a finding which may reflect either loss of the normal cerebellar inhibition (Baloh *et al.*, 1986), or an adaptive mechanism for stabilization of gaze in response to impaired optokinetics and smooth pursuit function (Zee *et al.*, 1976). Evidence against the latter possibility is that the gain increase is usually not as prominent at low frequencies where it would be expected to be of most use in compensation for loss of the visual following reflexes (Baloh *et al.*, 1986). An interesting finding was the similar levels of VOR gain in patients and controls when active head movements were used to produce the response, implying that the higher estimates of VOR gain seen with passive whole body rotation in the cerebellar patients may not be indicative of the levels of compensatory eye movement gain associated with natural head movements. It is possible that, during active movements, the cervico-ocular reflex (COR) is used to modulate this increase in VOR gain (Thurston *et al.*, 1987), so that gaze stability is preserved during head-free pursuit. However, cerebellar lesions are known to impair the ability to adapt the VOR (Robinson, 1976), and our patients were unable to modulate the gain of the VOR using imagined fixation targets in darkness, so it seems unlikely that they were directly modifying the actual VOR gain. Rather, it seems more likely that cerebellar disease results in disinhibition of the COR, just as it does to the VOR in some patients, and the summation of the two responses during active head movements produces the resultant compensatory eye movement gain.

In support of this, it has been demonstrated that the COR gain may be increased in some patients with cerebellar disease (Thurston *et al.*, 1987; Bronstein and Hood, 1985), and the COR may function in either a compensatory or anti-compensatory fashion with respect to the VOR in normal subjects (*see* Jürgens and Mergner, 1989, for review), although we did not test this in our patients. The COR is not thought to influence the pattern of the compensatory eye movement response during active head movements at higher frequencies (i.e above 1 Hz), in which situation an abnormal VOR gain may produce oscillopsia in patients with cerebellar disease (Gresty *et al.*, 1977). In contrast, at lower frequencies, we have found that these patients are able to cope well with the potential gaze disturbances produced during active head movements.

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SACCADIC REACTION TIMES IN PATIENTS WITH FRONTAL AND PARIETAL LESIONS

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SUMMARY

The effect of unilateral circumscribed lesions in different areas of the frontal and parietal cortex on the distributions of saccadic reaction times (SRTs) was investigated in 32 patients under four stimulus conditions: (i) *gap-random*: a target light appeared 200 ms after extinction of a central fixation light randomly at 8° either left or right; (ii) *overlap-random*: like (i), but the fixation light remained on ('overlap'); (iii) *gap-simultaneous*: two peripheral lights appeared simultaneously left and right 200 ms after the extinction of the fixation light, one predesignated by instruction as saccadic target; (iv) *overlap-simultaneous*: like (iii), but the fixation light remained on. Depending on SRT and condition and based on the data of control subjects, we evaluated the percentages of anticipatory (SRT: 0-90 ms), express (91-157 ms) and regular (158-400 ms) saccades, of time (>400 ms) and direction errors as well as the mean latencies and the standard deviations. These data were compared across control subjects, frontal lobe patients with a lesion in the region of the frontal eye field (FEF), and frontal patients with a lesion outside the FEF, as well as across control subjects, parietal lobe patients with a lesion in the dorsolateral region, and parietal patients with a lesion outside the dorsolateral region.

(i) Frontal patients with a lesion in the FEF region showed an increased percentage of express saccades (gap-random condition), especially with saccades directed towards the side of the lesion (ipsilateral). If fixation was not interrupted prior to target appearance (overlap-random), express saccades were largely suppressed, similar to normals. All patients with a frontal lesion, whether in the region of the FEF or not, showed a decreased percentage of contralateral anticipatory saccades (gap-simultaneous), whereas the percentages of direction and time errors were in the normal range, even if more than one stimulus was presented (e.g. overlap-simultaneous condition). (ii) Patients with dorsolateral parietal lesions showed decomposed SRT patterns (high SRT variability, increased percentages of time and direction errors, decreased percentages of express and anticipatory saccades). The decomposition had a contralateral preponderance and increased if more than one stimulus was visible beside the saccadic target.

Our results suggest that FEF lesions impair mainly the volitional control over visually triggered express or reflex-like saccades if fixation is disrupted, whereas dorsolateral parietal lesions impair mainly the selection of the visual targets.

INTRODUCTION

Many brain areas have been shown to participate in the generation of saccades, including areas of the occipital, parietal and frontal cortices; the exact role of these cortical areas, however, has not been well established.

Ferrier (1876) originally showed in the monkey that electrical stimulation of a region in area 8, the 'frontal eye field', evokes contralateral eye movements. These eye movements are indistinguishable from the monkey's own spontaneous saccades

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(Robinson and Fuchs, 1969; Bruce *et al.*, 1985). Also in humans electrical stimulation of the frontal eye field (FEF) produces conjugate eye movements to the contralateral side, occasionally associated with head movements in the same direction (Foerster, 1936; Rasmussen and Penfield, 1948; Godoy *et al.*, 1990). Similar movements may be found in patients, in whom this region is irritated by some pathological process or is the focus of epileptic activity (Foerster, 1936). An acute lesion of the FEF (e.g. by a stroke) produces, besides an ipsilateral deviation of eyes and head, an immediate but transient neglect of objects in the contralateral visual field (Luria *et al.*, 1966; Hoyt and Daroff, 1971; Heilman and Valenstein, 1972; Watson *et al.*, 1978; Damasio *et al.*, 1980) and an incapacity to perform voluntary or 'command' eye movements (Holmes, 1938). Similar observations were made in several lesion studies in monkeys (Kennard and Ectors, 1938; Welch and Stuteville, 1958; Latto and Cowey, 1971*a*,*b*; Schiller *et al.*, 1980, 1987). Electrophysiological recordings in the FEF of monkeys have revealed that the discharge of many neurons is correlated with saccadic eye movements and fixation (Wurtz and Mohler, 1976; Goldberg and Brushnell, 1981; Bruce and Goldberg, 1985; Segraves and Goldberg, 1987). Taken together, these findings suggest that the FEF represents an important cortical structure for the initiation and control of voluntary saccades.

However, complete destruction of the FEF seems to have minimal long-lasting effects on visually guided saccades (Kennard and Ectors, 1938; Lynch, 1987). Schiller *et al.* (1980, 1987) showed that, after bilateral removal of either the FEF or the superior colliculus (SC), monkeys were still able to make accurate saccades. Combined lesions of both FEF and SC were required to attenuate voluntary saccades permanently beyond a small central region. These findings suggest that eye movement control signals can reach the oculomotor centres in the brainstem on at least two neural circuitries, one involving the SC and the other the FEF. The existence of parallel pathways would also explain the fast recovery after FEF lesions.

Ferrier (1876) also described an 'occipital eye field', which according to Vogt and Vogt (1919) comprises areas 19a and 7a. While area 19a is considered now mainly a visual area, area 7a and adjacent cortical areas contain neurons that discharge in association with saccades (Hyvärinen and Poranen, 1974; Mountcastle *et al.*, 1975; Robinson *et al.*, 1978; Andersen *et al.*, 1987). In the monkey, Ferrier's original finding was confirmed in several stimulation studies (Vogt and Vogt, 1919; Walker and Weaver, 1940; Fleming and Crosby, 1955; Wagman, 1964; Kurylo and Skavenski, 1991). Compared with the FEF or SC the elicitation of saccades in area 7a is more inconsistent and the threshold current is higher (Shibutani *et al.*, 1984). Subdivisions within the posterior parietal cortex appear to serve different functions for visual perception and eye movements (*cf* Andersen, 1989). The lateral intraparietal area, which projects to the FEF and the SC (Barbas and Mesulam, 1981; Lynch *et al.*, 1985) seems to participate in the programming of spatial coordinates of intended saccades (Gnadt and Andersen, 1988; Duhamel *et al.* 1992), whereas area 7a appears to contain neural substrates for directing visual attention to objects of interest in extrapersonal space (Mountcastle *et al.*, 1975; Lynch *et al.*, 1977; Robinson *et al.*, 1978; Bushnell *et al.*, 1981; Lynch and McLaren, 1989).

In humans, lesions of the posterior parietal cortex may lead to disturbances in visual spatial orientation and attention, which cannot be explained by a sensory visual deficit (Bàlint, 1909; Holmes, 1918; Brain, 1941; Denny-Brown *et al.*, 1952; Crichley, 1953;

Posner *et al.*, 1984, 1987). With respect to visually guided saccades, an inability or slowness to change the direction of gaze voluntarily has been reported (Luria *et al.*, 1963; Karpov *et al.*, 1968; Chédru *et al.*, 1973; Girotti *et al.*, 1983; for prolonged saccadic reaction times (SRTs), *cf* Sundqvist, 1979; Pierrot-Deseilligny *et al.*, 1987). However, during routine neurological testing, most patients with subacute or chronic parietal (or frontal) lesions do not show any overt deficit in the performance of saccadic eye movements.

Recent studies suggest that the assessment of eye movement deficits following circumscribed cortical lesions may require tests that are specific for certain types of saccadic eye movements. In monkey, for instance, FEF lesions do not effect visually triggered saccades, but may impair saccades to remembered (Deng *et al.*, 1986) or expected (Bruce and Borden, 1986) target locations. Guitton *et al.* (1985) found that human patients with unilateral removal of frontal lobe tissue correctly performed saccades to a suddenly appearing visual stimulus, but had severe difficulties suppressing reflex-like saccades towards this stimulus when instructed to execute a saccade into the opposite, stimulus-free hemifield (anti-saccade task).

In the present study, we investigated in humans the effects of subacute or chronic unilateral frontal and parietal lesions upon the generation of saccades. We used four different stimulus conditions, by which we intended to test specific aspects of the saccadic eye movement system. We evaluated mean SRTs, but placed the emphasis of our approach on a distinction between different types of saccades, which we tried to classify on behalf of their SRT distributions and the stimulus condition in which they were elicited. Also, we assessed the percentages of direction errors as well as time errors (SRTs exceeding a certain time limit). In particular, we concentrated on the following four questions:

(i) How do cortical lesions affect the occurrence of saccades with very short SRTs, which in normals are found mostly when fixation is disrupted prior to stimulus appearance? It is known that a remarkable shortening of mean SRT occurs in healthy subjects if a pause of 200–300 ms is introduced between the termination of a fixation point and the appearance of a peripheral target ('gap paradigm'; Saslow, 1967). Studying SRTs in monkeys, Fischer and Boch (1983) observed that under gap conditions the distribution of SRTs becomes bimodal with the faster mode peaking around 70–80 ms (express saccades) and a slower mode at about 140–160 ms (regular saccades). Later it was found that humans also produce short-SRT saccades ($\approx$ 100 ms) under gap conditions, which probably correspond to the express saccades of monkeys (Fischer and Ramsperger, 1984, 1986). The majority of these saccades cannot be considered to be anticipatory (Kalesnykas and Hallett, 1987). For comparison, in the frontal patients of Guitton *et al.* (1985) the uncontrolled reflex-like saccades had SRTs of 80–140 ms, which is similar to the SRTs of the express saccades. We therefore wondered what the SRTs of the patients with frontal lesions would be in the gap paradigm.

(ii) To what extent does the presence of a fixation point at the time of the target appearance (overlap condition) affect the occurrence of short-SRT saccades? A similarity between the SRT ranges of express saccades of healthy subjects and reflex-like saccades of patients do not necessarily imply that both represent the same type of oculomotor response. However, further evidence for this notion may possibly be obtained if their occurrence shows a similar modification by changes in the state of fixation. In normals express saccades are largely suppressed with the overlap condition, even if their number has been considerably increased in the gap condition after extensive training (Fischer and Ramsperger, 1986). The disruption of fixation itself, however, seems not to be a necessary premise to obtain express saccades, because they can also be obtained if the subject is instructed to foveate the fixation light, but not to fixate it 'attentively' (Mayfrank *et al.*, 1986). With the gap condition a bilaterally prolonged mean SRT has been found in human patients with posterior parietal lesions, while a decrease was found with FEF lesions (Pierrot-Deseilligny *et al.*, 1987). We therefore wondered what the suppression effect of fixation would be in patients with frontal or parietal lesions.

(iii) To what extent do the same cortical lesions affect the generation of anticipatory saccades which occur if a target is expected at a known target location? This question was motivated by the finding that in monkeys unilateral FEF lesions affect saccades to remembered target locations in the contralateral hemifield (Deng *et al.*, 1986). Also, neurons in the lateral intraparietal area are active during preparation of memory-guided saccades (Gnadt and Andersen, 1988). In human patients, a prolonged mean SRT of such saccades has been associated with frontal and parietal lesions (Pierrot-Deseilligny *et al.*, 1991).

(iv) What is the effect of these lesions on the selection of the saccadic target among simultaneously presented visual stimuli? Studies in patients with parietal lesions have suggested a specific impairment to select between several, simultaneously presented targets (Denny-Brown *et al.*, 1952; Heilman *et al.* 1985). This led us to study the effect of cortical lesions on saccadic target selection under conditions in which beside a saccadic target other visual stimuli were presented at the same time.

The results we obtained with this approach supported our notion that the assessment of specific aspects of saccadic behaviour may help to disclose impairments of patients with chronic cortical lesions, in whom routine oculomotor examinations or simple mean SRT measurements reveals only minor, if any disturbances.

SUBJECTS AND METHODS

Subjects

Preselection

On the basis of computerized tomographic (CT) brain scans 55 patients were preselected by the following criteria: (i) a circumscribed cortical lesion in one hemisphere, located in, or extended into, either the frontal or the parietal lobe; (ii) clear demarcation of the lesion from the surrounding tissue (as a rule, hypodensity of <15 HE); (iii) absence of a considerable oedema in, or pressure exerted on, the surrounding tissue; (iv) sparing of the deep white matter underlying the lesion (in order to avoid involvement of pathways from remote cortical fields).

Final selection

Preselected patients, who gave informed consent to participate in the experiments, underwent a thorough neurological examination including neuropsychological testing. The following selection criteria were used: (i) a good state of general health, no severe disability in the activities of daily living, self-maintenance, full orientation, no psychiatric history, ability to walk; (ii) no visual field deficits; (iii) normal or almost normal visual acuity; (iv) no extinction phenomenon detectable with visual and somatosensory testing, normal line-crossing test of Albert (1973); (v) no deficit of body scheme or spatial orientation (finding the patient's own room in the clinic and/or the laboratory on second visit); (vi) absence of aphasic disorders which would disable verbal communication to a considerable degree; (vii) absence of oculomotor deficits in clinical testing and electronystagmography; (viii) subacute or chronic state of the lesion (desired time interval between testing and lesion ≥1 wk).

Thirty-two patients, aged 25–69 (mean 47) yrs, fulfilled the criteria with the following exceptions. (i) In two patients, the interval between lesion and testing was 4 d and 6 d, respectively. However, both were in good condition and showed no neurological or neuro-psychological disorders. Three patients were tested before tumour operation. (ii) One patient with a right dorsolateral parietal lesion had a homonymous scotoma in the outer 40° of her left-side visual field. (iii) Three of the patients with a pericentral lesion and two patients with a parieto-dorsolateral lesion revealed slight somatosensory deficits

None of the patients showed signs of cerebellar or brainstem involvement. Thirty patients were right handed and two were left handed on enquiry. In Table 1 clinical descriptions are given for all 32 patients. All patients were naive with respect to the design and the goal of the study.

Classification of lesions

The topography and the extent of each lesion was defined in all selected patients by CT scans (horizontal routine slices of 10 mm thickness, performed with an angulation of 10° relative to the epicantho-meatal line). The outlines of each lesion were transferred on 10 schematic brain templates, taken from the CT

TABLE 1. CLINICAL DATA OF PATIENTS

Case no	*Age (yrs)*	*Sex*	*Type of lesion*	*Side*	*Region*	*Interval (recording-lesion)*	*Pareses (manifest)*	*Sedating medication*
1	57	F	Stroke	R	fronto-dorsol	31 d	Facial (L)	X
2	43	M	Stroke	R	fronto-dorsol	14 d	Facial (L)	
3	56	M	Tumour	R	fronto-dorsol	6 d		
4	26	M	Tumour	L	fronto-dorsol	Before op		
5	33	F	Tumour	R	fronto-polar/dorsol	30 d		X
6	42	F	Tumour	R	fronto-polar/dorsol	26 d		X
7	34	M	Contusio	L	fronto-polar	20 yrs		
8	55	M	Abcess	R	fronto-polar	15 yrs		
9	34	F	Tumour	R	fronto-polar	3 yrs		
10	25	M	Tumour	R	fronto-polar	4 yrs		X
11	66	M	Tumour	R	fronto-polar	10 d		X
12	58	F	Bleeding	L	fronto-polar	10 d		
13	35	M	Tumour	L	fronto-medial	9 d		X
14	29	M	Tumour	L	fronto-medial	Before op		X
15	45	M	Tumour	R	fronto-medial	Before op		
16	66	F	Stroke	R	pericentral	180 d		
17	23	M	Bleeding	L	pericentral	7 d	Hemiparesis (R)	
18	30	M	Stroke	L	pericentral	7 d	Hemiparesis (R)	
19	46	F	Tumour	L	pericentral	15 d	Hemiparesis (R)	
20	56	M	Tumour	L	pericentral	13 d	Hemiparesis (R)	
21	61	M	Tumour	L	pericentral	14 d	Hemiparesis (R)	
22	55	M	Tumour	R	parieto-dorsol	29 yrs		X
23	64	M	Stroke	R	parieto-dorsol	6 yrs		
24	62	F	Stroke	R	parieto-dorsol.	5 yrs		
25	53	M	Stroke	L	parieto-dorsol	35 d		
26	62	F	Stroke	R	parieto-dorsol	20 d		
27	60	M	Stroke	R	parieto-dorsol	17 d		
28	69	M	Tumour	R	parieto-dorsol	19 d		
29	69	M	Stroke	L	parieto-dorsol	10 d		
30	35	F	Tumour	L	parieto-medial	21 d		X
31	27	F	Stroke	L	parieto-medial	8 d		X
32	28	M	Tumour	R	parieto-medial	4 d		

Clinical data of the 32 selected patients The table gives the number given to each patient, his/her age and sex, the aetiology of the lesion, the side of the lesioned hemisphere, the classification of the lesioned region, the time interval between lesion and testing, the incidence of motor pareses and the incidence of potentially sedating medication (e.g. antiepileptic drugs).

atlas of Nadjmi *et al.* (1981). In order to compare the effect of differently located lesions in the frontal and parietal lobe, we parcellated them into six regions, with respect to neurophysiological and anatomical aspects. Figure 1 shows the parcellation of the frontal and parietal lobes into different regions on the 10 templates. We distinguished between the following regions:

Frontal lobe. (i) Region of interest (FEF region): dorsolateral frontal cortex (lateral parts of Brodmann's areas 6 and 8 as well as posterior borders of areas, 9, 44 and 46), which includes the region of the FEF (Melamed and Larsen, 1979; Fox *et al.*, 1985); patients were considered to belong to this particular group if their lesion was located in, or extended into, this region. (ii) Frontal regions adjacent to the FEF: the three regions located anteriorly, medially and posteriorly to the FEF, which comprised the polar-basal cortex (areas 9–12, anterior parts of areas 32 and 44–47), the medial frontal sites [medial parts of areas 6 and 8, posterior parts of areas 24 and 32, the supplementary motor area (SMA) is located in this region (Penfield and Welch, 1951)] and the pericentral cortex (area 4 and adjacent parts of area 6; all pericentral lesions also reached into the parietal lobe; *cf below*).

Parietal lobe. (i) Region of interest: dorsolateral parietal cortex (lateral and dorsal parts of area 7, adjacent parts of areas 19, 39 and 40); this region includes the parietal eye field. (ii) Parietal regions adjacent to the parietal eye field region: the medial parietal cortex (medial parts of area 7 and posterior parts of areas 23 and 31) and the pericentral cortex (areas 1–5 and adjacent parts of area 7; the pericentral lesions extended also into the frontal lobe).

Figure 2 shows for all 32 patients, sorted according to the parcellation (Fig. 1), the location and the extension of their lesion. In four patients, the lesions were essentially restricted to the frontal region of interest (Fig. 2A), while in two other patients the lesion was more anteriorly located, but extended well into it (Fig. 2B). The frontal lobe lesions of 15 patients did not extend into the region of interest: in six of these patients the lesion was essentially restricted to the fronto-polar/basal part (Fig. 2C), in three to the fronto-medial part (Fig. 2D) and in six patients to the pericentral part of the cortex (Fig. 2E). The pericentral lesions extended well into both the frontal and parietal lobes but never into the frontal and parietal regions of interest.

In the parietal cortex the lesions of eight patients were located in, or extended into, the parietal region of interest (Fig. 2F); in five of them the lesion was essentially restricted to this region. In nine patients the region of interest was not affected: beside the six patients with a pericentral lesion (Fig. 2E), three patients were tested with a lesion in the medial parietal cortex (Fig. 2G).

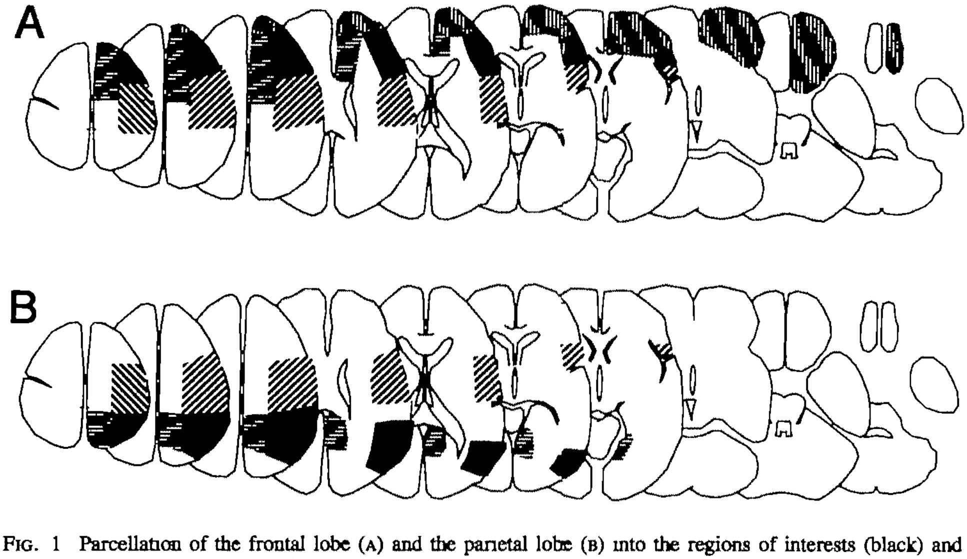

FIG. 1 Parcellation of the frontal lobe (A) and the parietal lobe (B) into the regions of interests (black) and into the adjacent frontal and parietal regions (stripes) used for the comparison. The topography and extent of these regions is given on 10 templates of serial horizontal brain slices

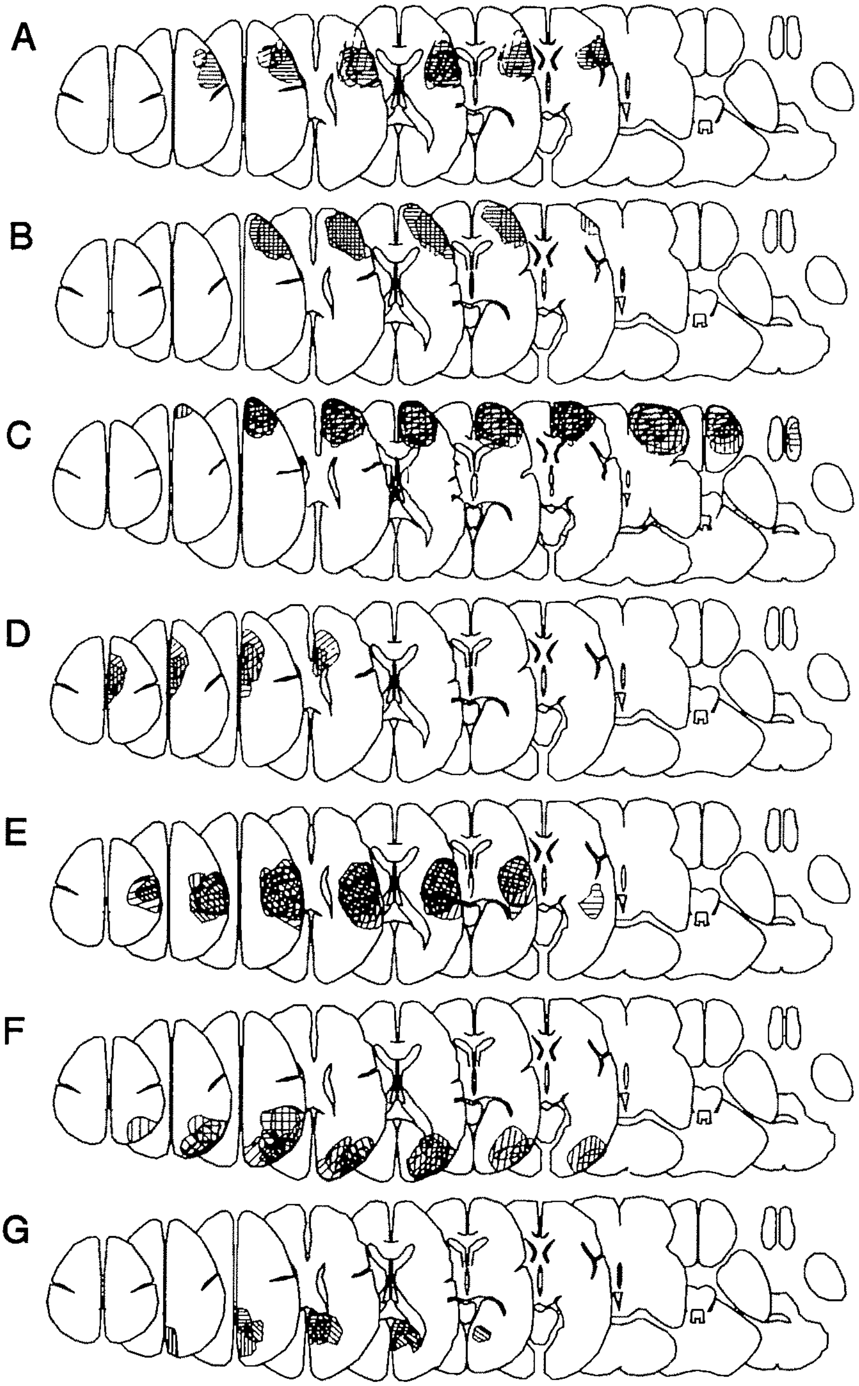

FIG. 2. Representative diagrams of all 32 lesions based on CT scans and separated according to the parcellation in Fig. 1 The outlines of the left-sided lesions were projected on the right side for comparison. A, lesions restricted to the frontal region of interest (FEF region). B, two lesions located more anteriorly to the FEF region, but extending well into this region. C, six fronto-polar/basal lesions. D, three fronto-medial lesions. E, six pericentral lesions. F, eight lesions in the parietal region of interest (dorsolateral parietal cortex) G, three lesions in the medial parietal cortex.

Control subjects. Seventeen subjects (mean age 42.1 yrs; 11 males, 6 females), who were either paid volunteers or patients hospitalized with non-neurological disease, served as controls. Each subject had normal or almost normal visual acuity, no oculomotor disorder, no history of neurological or psychiatric dysfunction and was not taking any medication known to affect the oculomotor system. They were naive with respect to the experiments performed. The control subjects gave their informed consent before the experiments.

Apparatus and experimental design

Horizontal movements of the left eye were recorded using an infrared scleral reflection technique (modified after Gauthier and Volle, 1975) with a resolution of 0.25°. The eye position signal was fed into an electronic velocity threshold circuit, which detected the onset of rapid position changes. The threshold detector stopped a millisecond-counter triggered by target onset. The resulting SRT was recorded by a laboratory computer for later analysis. Eye and target position were also displayed on an oscilloscope for visual inspection of each trial. Artefacts (e.g. eye blinks) and direction errors were excluded on-line from the data collection. The number of direction errors, however, was separately noted. Saccadic reaction time frequency histograms were constructed on-line on a terminal screen using a bin width of 10 ms (internal bin resolution, 2 ms; time of analysis, 600 ms after target onset).

The subjects were seated in a darkened room with their heads restrained by a head support at a distance of 70 cm from a screen, on which a central fixation light and two eccentric target lights were presented along a horizontal line at eye level (three red light-emitting diodes, LEDs; visual angle: 0.25°; luminance approximately 30 cd/m^2). The target lights were located 8° left and right from the fixation point. The temporal sequence of the stimulus presentation was controlled by a computer.

Stimulus conditions (Fig. 3)

Gap-random condition. The fixation light was presented for 2000 ms and then extinguished. After a gap of 200 ms one of the two target lights appeared randomly either on the right- or the left-hand side. In all experiments the target was presented for 1500 ms. After a randomly varied inter-trial period of

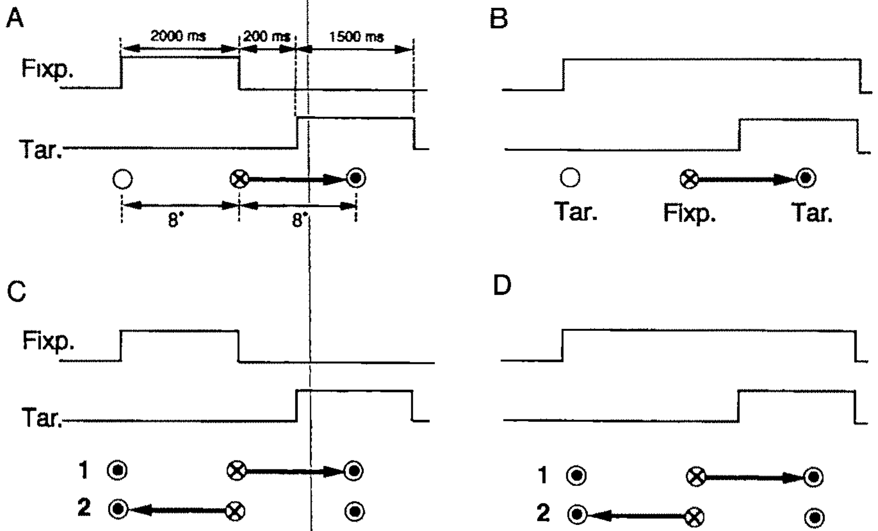

FIG. 3. Schematic representation of the time sequences and the stimulus displays for the four stimulus conditions used. A, gap-random: the central fixation light (Fixp.) was extinguished 200 ms prior to the onset of the target (Tar.), which appeared either to the right or left at 8° eccentricity B, overlap-random: analogous to gap-random, but the fixation light remained on. C, gap-simultaneous: after the extinction of the fixation light two eccentric lights appeared simultaneously, one of them was predesignated as the target. D, overlap-simultaneous: analogous to gap-simultaneous, but the fixation light remained on

1500 – 1900 ms, the next trial was started automatically. Subjects were instructed first to look at the fixation point and to change the direction of gaze only after the target had appeared.

Overlap-random condition. As in the gap-random condition, one of the two peripheral target lights appeared 2000 ms after fixation light onset, but the fixation light was not extinguished (overlap). The instructions were the same as in the gap-random condition.

Gap-simultaneous condition. The time sequence was analogous to that of the gap-random condition, but instead of one peripheral light both the left and right light appeared simultaneously. Two sets of trials were performed; in one set, subjects were instructed to look always to the right LED, in the other set they were instructed to look to the left LED. The LED on the contralateral side with respect to the target was to be ignored. Note, that in this condition the target location was known and the target onset could be predicted from the offset of the fixation light.

Overlap-simultaneous condition. The procedures were analogous to those of the gap-simultaneous condition, but the fixation light remained on during presentation of the two peripheral lights (overlap). In this experiment subjects also knew the target location but the time of its appearance was not announced.

Procedure

Before experimental testing, detailed instructions regarding the trial sequence and the meaning of the stimuli were given. Each subject received a few practice trials. Seventy-five SRTs (minus the number of direction errors) were collected for each condition and saccade direction. The four conditions were performed in two sessions on two different days. In one session the random conditions were tested, in the other session the simultaneous conditions were tested. The order of the sessions and of the two conditions in each session was randomized. Each session lasted about 1 h and was interrupted by one or more rests of several minutes.

Data analysis

According to their latencies, saccades were divided into four groups: anticipatory saccades (SRT range: 0–95 ms); express saccades (96 – 157 ms); regular saccades (158 – 400 ms); time errors (SRT > 400 ms). A fifth group comprised saccades initiated into the wrong direction (directions errors). To measure only SRTs of the main saccades, saccades that were clearly dysmetric (amplitudes of <80% or >120% of the target's distance) were discarded. The following criteria, which were based on the results of our normal controls (*cf* Results), were used for each class of saccades:

Anticipatory saccades. Saccades with SRTs within a range of 0–95 ms. Saccades with wrong direction were counted as direction errors. Analysis of this saccade class was restricted to the two simultaneous conditions in which the target location was predesignated. In the two random conditions, the few saccades falling into this SRT range were discarded.

Express saccades. Under gap conditions, histograms that included a large number of SRTs tend to be bimodal with the first peak (express saccades) occurring at 120 ms and the second peak (regular saccades) at about 160 ms, when target location is randomized and a given stimulus luminance is used (Fischer and Ramsperger, 1984, 1986; Wenban-Smith and Findlay, 1991). Grand averages are often unimodal due to inter-individual variations of the peaks (*cf* Fig. 7). Our samples of 75 SRTs of saccades in each direction was too small to clearly separate express from regular saccades in distributions from single subjects. The collection of a larger number of SRTs, however, was not feasible with our patients. We therefore collected 300 saccades for each condition and saccade direction in four normal subjects and determined the corresponding SRT ranges. These measures provided a range of 96 – 157 ms for express saccades in the random conditions. Since anticipatory saccades may well reach into the range of 96 – 157 ms, we disregarded this express SRT range with the simultaneous conditions and analysed express saccades only with the random conditions, where anticipatory saccades are rare (Kalesnykas and Hallet, 1987; Wenban-Smith and Findlay, 1991).

Regular saccades. According to the data of our four control subjects, these saccades fell into the range of 158 – 400 ms. Since they appear to represent an inhomogeneous group ('fast' and 'slow' regular saccades; Fischer, 1987), we only considered the mean and the standard deviation of these SRTs.

Time errors. The classification of saccades with SRTs >400 ms as 'time errors' was motivated by the observation that such long-latency saccades were rare in our control subjects (*cf* Results and Table 2) and our assumption that saccades with very long SRTs might not be visually guided.

Statistical analysis

The following measures were evaluated: (i) percentages of each saccade type in the individual SRT distributions as well as direction errors; (ii) mean SRT across the range of 0–400 ms ($M_{0-400\ ms}$) and its standard deviation ($SD_{0-400\ ms}$); (iii) mean SRT and standard deviation across the range of 158–400 ms ($M_{158-400\ ms}$ and $SD_{158-400\ ms}$, respectively)—this measure essentially comprises only regular saccades and excludes anticipatory and express saccades as well as time errors.

These measures were taken for each subject, condition and saccade direction separately and served for inter-condition comparisons (gap versus overlap and random versus simultaneous conditions) as well as inter-group comparisons. For these comparisons, we first used a parametric approach for global analysis of all effects involved (inter-condition and inter-group differences as well as interactions; BMDP2V, analysis of variance with repeated measures). In order to verify the inter-group differences thus obtained, we applied a non-parametric test (Kruskal-Wallis test, SAS procedure NPAR1WAY) for each measure, condition and saccade direction separately. These tests were performed as multiple test procedures; in a first step, the null hypothesis (all groups are equal) was tested. In case of a significant difference, the second step was used to perform pairwise comparisons at the same significance level. Similarly, some inter-condition differences were verified by a Wilcoxon (signed rank) test (BMDP35).

The inter-group comparisons comprised the following parts: (i) comparison across the patients with frontal lesions in the region of interest (FEF region), the patients with frontal lesions that spared this region and the control subjects; (ii) comparison across the patients with parietal lesions in the region of interest (dorsolateral parietal cortex), the patients with parietal lesions that spared this region and the control subjects; (iii) comparison across the two patient groups with lesions in the region of interest and control subjects.

The mean age of our normal controls (42 yrs) matched that of our patients (47 yrs), but between patient groups mean age differences were often large. It is known that SRTs in adults increase with age, whereas the accuracy of 5–20° saccades remains unchanged (Abel *et al.*, 1983; Warabi *et al.*, 1984; Hotson and Steinke, 1988). Similar findings were obtained in our control subjects, Therefore, in cases where the ages differed considerably, we compared across the groups in addition by superimposing the above measures and deciding by visual inspection whether the findings could be related to an age effect. No age effects were apparent in these cases.

RESULTS

Control subjects

The four different stimulus conditions resulted, as expected, in specific changes of the SRT distributions. The SRT distributions of one representative control subject are shown in Fig. 4A. With the gap-random condition, the majority are regular saccades (SRT: 158–400 ms) preceded by a small peak of express saccades (96–157 ms). In contrast, in the overlap-random condition there are mainly regular saccades and nearly no express saccades. Note that in these two conditions essentially no anticipatory saccades occurred. In the gap-simultaneous condition, in contrast, about half of the saccades are anticipatory (0–95 ms), and regular saccades are quite rare. In the overlap-simultaneous condition, finally, mainly regular saccades are obtained with only few anticipated saccades. The outlines of the grand average SRT distributions of the normal controls are shown in Fig. 7. The results of our control subjects with the two random conditions were consistent with previous studies (Fischer and Ramsperger, 1984, 1986; Kalesnykas and Hallet, 1987; Wenban-Smith and Findlay, 1991).

With all four conditions, no major left-right differences were obtained. Nevertheless, two comparisons were performed. We compared the patients saccades to the side of the lesion (ipsilateral saccades) first with the rightward saccades and then with the leftward saccades of the control subjects, and did the same for the patients contralateral saccades.

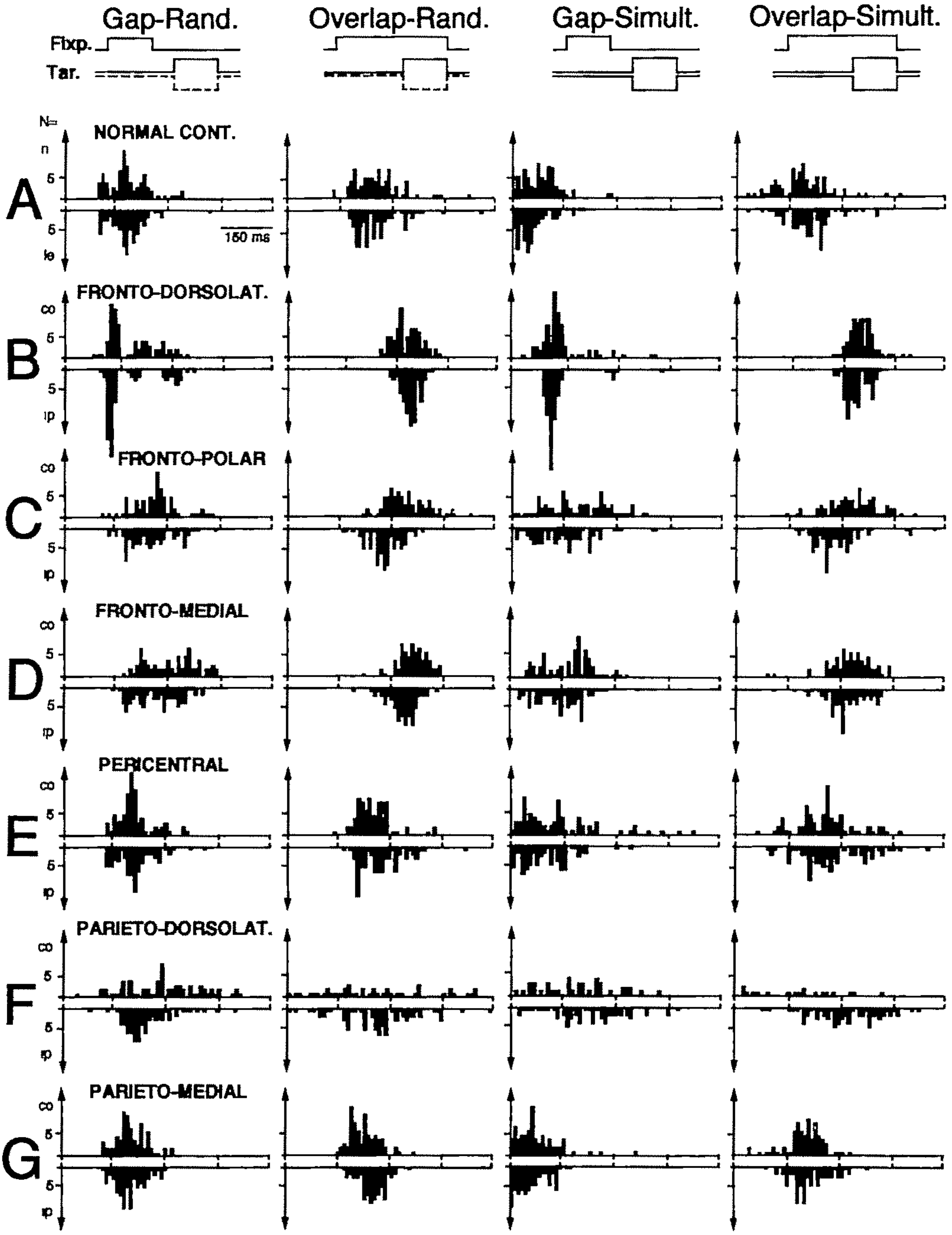

FIG. 4 Saccadic reaction times distributions of a control subject (A) and six representative patients with differently located lesions (B–G) for the four tasks indicated schematically on the top. B, patient no. 3 in Table 1, FEF lesion; C, no 8, fronto-polar lesions; D, no. 13, fronto-medial lesion; E, no. 20, pericentral lesion; F, no 25, dorsolateral parietal lesion; G, no. 31, medial parietal lesion. The number of saccades (ordinates) is plotted as a function of the SRT (abscissas). Saccades to the right (ri)/contralateral (co) side are shown above the x-axis, those to the left (le)/ipsilateral (ip) side below the x-axis.

The main results from the control subjects and the patients on which the statistical analysis was based are shown in Table 2.

Frontal lesions

The differences obtained with the inter-condition comparisons for the group of patients with dorsolateral frontal lesions (FEF patients) and the group of patients with frontal lesions that spared this region (non-FEF patients) were qualitatively similar to those of the control subjects described above. Yet, there were quantitative differences, which we describe for the more instructive inter-group comparisons.

Figures 4B – E gives examples of the SRT distributions of patients with frontal lesions for the four stimulus conditions. In the gap-random condition, the SRT distribution of the FEF patient (Fig. 4B) shows a pronounced peak in the express range (SRT: 96 – 157 ms) for both contralateral and ipsilateral saccades. In contrast, only small peaks are seen in this range with the control subjects (Fig. 4A) and the patient with pericentral lesion (Fig. 4E), and none with the two patients in whom the frontal lesions was outside the FEF (Fig. 4C,D). For comparison, in the overlap-random condition express saccades are either sparse or almost absent in the SRT distributions of these five subjects, but some differences are seen with respect to the regular saccades (158 – 400 ms). In the gap-simultaneous condition, a considerable number of anticipatory saccades (0 – 95 ms) is seen in the distributions of the four patients and the control subject. However, they are clearly more frequent in the control subject (Fig. 4A) and the patient with the pericentral lesion (Fig. 4E) than in the three patients with the frontal lesion (Fig. 4B – D). In the overlap-simultaneous condition, the SRT distributions in these frontal patients (Fig. 4B – D) appear to be shifted somewhat towards higher SRT values as compared with the control subjects (Fig. 4A), but this was not the rule (compare in Table 2 the mean SRT ± SD values in the overlap-simultaneous condition between subject groups C and A). Note, finally, that the SRT distributions of the FEF patient (Fig. 4B) in the gap-simultaneous condition appear to contain mostly express saccades (not considered in our quantitative analysis, however).

In Fig. 5A – D the main results of the inter-group comparisons are given separately for contralateral (patients) versus rightward (control subjects) and ipsilateral versus leftward saccades (the reverse comparisons yielded the same results).

Gap-random condition. In this condition the percentage of express saccades was increased in the FEF patients as compared with both other groups (χ^2: 15.71) as well as in the pair-wise comparison to non-FEF patients (12.29) and to control subjects (12.3). This effect was significant only for ipsilateral saccades, but it was also very plain for contralateral saccades in the individual SRT distributions of three out of six FEF patients. In the group of non-FEF patients, the percentage of ipsilateral express saccades was slightly less than in normals.

Overlap-random condition (not shown). In this condition the percentage of express saccades was on the average decreased by a factor of 6 in the normal controls, by a factor of 9 in the FEF patients, and by a factor of 15 in the non-FEF patients. Despite the fact that FEF patients had considerably higher percentage values in express saccades in the gap-random condition than the other two groups, no statistically significant differences were found for the suppression of express saccades by the stimulus overlap between the three groups.

TABLE 2 NUMERICAL DATA

		%Expr.	%Antic.	%TimeE	%Dir.E	0–400 ms		158–400 ms	
						Mean	*±SD*	*Mean*	*±SD*
(A) Normal controls									
Left	GR	25±15				192±22	43±15	223±36	41±15
	OR	5±7				254±28	50±13	274±30	47±10
	GS		48±13.5	5±5	<3	107±30	68±22	218±26	43±19
	OS		5±4.2	3±3	<3	224±28	65±8	253±23	49±8
Right	GR	18±13				198±18	44±11	225±31	41±14
	OR	2±3				268±26	49±9	285±20	50±9
	GS		48±18	5±7	<3	109±36	66±18	216±32	37±16
	OS		5±6	3±3	<3	235±33	63±12	265±27	48±6
(B) Frontal region of interest									
Ipsi	GR	66±9				157±15	42±19	204±29	40±13
	OR	8±11				250±63	50±18	263±54	47±18
	GS		32±19	2±2	<3	113±14	58±16	211±42	27±13
	OS		5±8	3±4	<3	237±64	58±22	254±46	43±14
Contra	GR	41±32				177±23	45±19	209±19	40±12
	OR	4±8				280±44	50±18	289±38	43±11
	GS		21±19	7±7	<3	145±42	66±23	208±21	40±10
	OS		3±6	6±5	<3	254±59	47±19	265±52	38±13
(C) Frontal non-region of interest									
Ipsi	GR	14±13				219±33	47±11	229±27	42±15
	OR	1±2				278±32	45±8	285±35	45±10
	GS		34±21	5±7	<3	139±43	70±11	218±28	42±13
	OS		5±9	4±5	<3	250±43	55±19	265±33	45±9
Contra	GR	15±12				212±32	44±9	242±37	40±10
	OR	1±1				279±30	47±11	287±42	41±12
	GS		33±19	8±14	<3	135±38	69±15	219±31	48±27
	OS		4±7	7±9	<3	245±44	55±18	276±35	41±12
(D) Parietal region of interest									
Ipsi	GR	5±7				216±34	42±15	233±41	41±12
	OR	2±3				289±36	57±18	284±35	54±13
	GS		13±14	15±11	3±7	194±57	75±15	234±27	55±15
	OS		4±3	21±14	5±9	249±24	83±11	260±27	62±10
Contra	GR	7±6				245±34	60±15	252±37	48±17
	OR	2±3				288±39	65±18	295±32	56±14
	GS		13±10	24±11	27±24	199±64	89±21	251±44	45±11
	OS		5±5	12±16	36±32	242±70	89±22	279±30	52±9
(E) Parietal non-region of interest									
Ipsi	GR	16±13				210±22	46±7	224±23	39±12
	OR	1±1				285±22	46±7	294±31	41±5
	GS		48±19	5±5	<3	111±35	67±12	215±37	36±19
	OS		3±5	6±6	<3	247±26	61±20	266±28	46±12
Contra	GR	17±9				205±17	42±8	236±36	42±9
	OR	1±2				272±32	52±10	288±37	42±13
	GS		48±14	11±16	<3	115±30	73±16	215±36	51±34
	OS		4±5	4±4	<3	250±41	55±20	268±32	40±14

Numerical data of all subjects. Mean percentages of express saccades (%Expr.), anticipatory saccades (%Antic.), time errors (%TimeE), and direction errors (%Dir.E) as well as the means and their standard deviations (including the standard deviation values of both figures) separately for the SRTs between 0–400 ms and 158–400 ms for right and left saccades in the normal controls (A) and for ipsilateral (ipsi) and contralateral (contra) saccades in the patients (B–E). Stimulus conditions GR = gap-random; OR = overlap-random; GS, gap-simultaneous; OS, overlap-simultaneous.

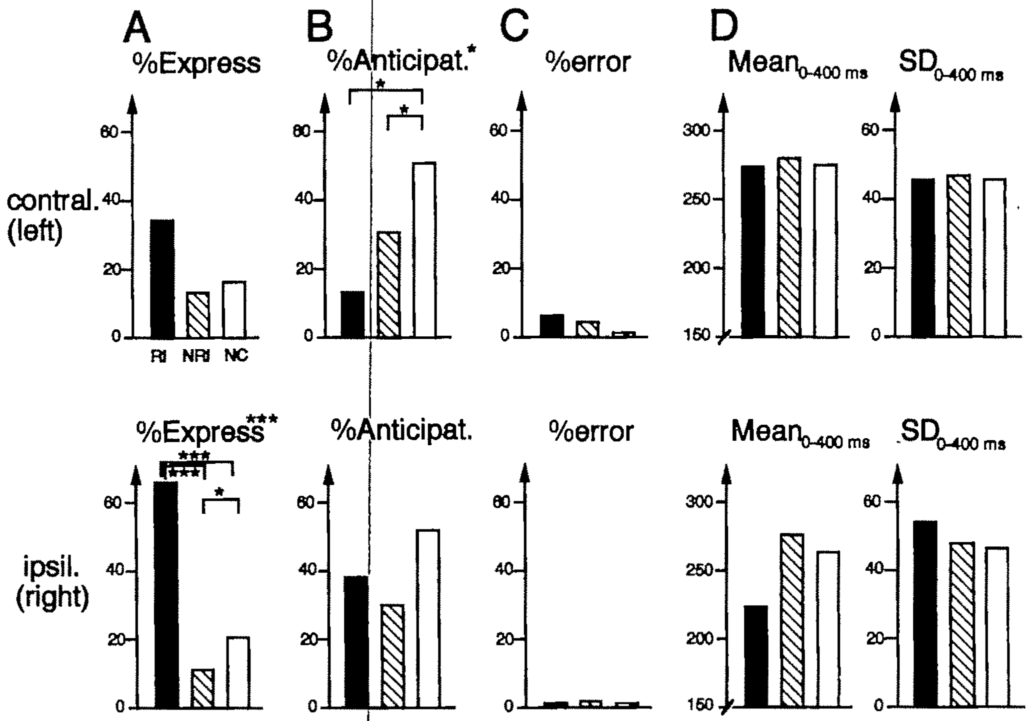

FIG. 5. Main statistical results of the frontal patients. Percentages of express saccades in the gap-random condition (A), anticipatory saccades in the gap-simultaneous condition (B), and time and direction errors in the overlap-simultaneous condition (C) as well as the means and the standard deviation (SD) in the overlap-random condition. Patients with a frontal lesion in the area of interest, RI (FEF patients), outside the area of interest, NRI (non-FEF patients), and the normal controls, NC. Asterisks on headings indicate significant differences in the multiple test procedures, while those above the brackets give the significance of the pairwise comparisons (*$P \leq 0.01$; **$P \leq 0.005$; ***$P \leq 0.001$). The columns give median values.

Gap-simultaneous condition. In this condition the percentage of contralateral anticipatory saccades was reduced in both patient groups, those with FEF lesions and those with non-FEF lesions, as compared with normal controls (χ^2: 10.22). The effect was somewhat weaker in the non-FEF patients (χ^2: 5.14) than in the FEF patients (7.47), but it became similar when we excluded the pericentral patients from this group.

Overlap-simultaneous condition. In this condition normal controls and FEF, as well as non-FEF, patients made few if any errors, and there were no significant differences across these three groups. The values given in Fig. 5c represent mainly time errors, since direction errors were hardly observed. Similar findings were obtained in the other three stimulus conditions.

Overlap-random condition. $M_{0-400\,ms}$ and $SD_{0-400\,ms}$ did not significantly differ across the three groups. Similarly in the gap-simultaneous and overlap-simultaneous conditions (not shown), no significant differences were found for these values. Thus, despite the fact that higher SRTs were suspected in some patients (*cf.* Fig. 4B–D), on average there was no considerable increase in SRTs in both patient groups with either of these three stimulus conditions. The $M_{0-400\,ms}$ of the FEF patients was significantly decreased with the gap-random condition. This finding could be accounted for, however, by the increased percentage of express saccades with this condition (the $M_{158-400\ ms}$ values were essentially similar across the three groups).

The subgroup of patients with pericentral lesions produced SRT distributions that were very similar to those of the normal controls. Therefore, this subgroup might have introduced some bias towards 'normal' in our group of non-FEF patients. In order to test this assumption, we compared the subgroup of pericentral patients with the control subjects. Indeed, no significant differences were found. As a consequence, we excluded the data of the pericentral patients from the non-FEF patient group and repeated the inter-group comparison. This comparison confirmed the above findings with one exception; in the overlap-random condition the non-FEF patients showed a slight increase in $M_{158-400\ ms}$ as compared with the control subjects and FEF patients.

When considering only non-FEF patients, who had lesions in the fronto-polar/basal region, the results were similar to those of the FEF patients, with the exception of the high frequency of express saccades in the latter. The grand average SRT distributions of these two groups of patients are shown in Fig. 7B and A, respectively (in A, patients nos 5 and 6 from Table 1 were excluded, since their lesions extended into both the FEF and the fronto-polar/basal region). Note that the SRT distributions are remarkably similar, apart from the express peaks in the FEF patients. Also, the results from the fronto/basal patients (nos 7 – 12) were similar to the three fronto-medial patients (nos 13 – 15; not shown), apart from a more pronounced decrease of anticipatory saccades in the fronto-medial patients with the gap-simultaneous condition.

A statistical comparison between patients with left hemispheric and those with right hemispheric lesions was not possible in both the group of non-FEF patients (after exclusion of the pericentral ones) and the group of FEF patients because of lack of numbers of patients. However, we can state that the percentages of both ipsilateral and contralateral express as well as anticipatory saccades in the two patients with lesion in the left fronto-polar cortex (*cf* Table 1) were similar to those of the four patients with right hemispheric lesions in that they were below those of the normal controls' mean values. Also, the percentages of ipsilateral and contralateral express saccades in the only patient with a lesion in the left fronto-dorsolateral cortex was similar to those of the five patients with right hemispheric lesions in that they were above those of the normal controls' mean values.

Taken together, all patients with a frontal lesion, whether in the FEF region or not, showed a decreased percentage of contralateral anticipatory saccades. In contrast, the percentages of direction and time errors were in the normal range, even if more than one stimulus was presented, as in the overlap-simultaneous condition. Frontal patients with a lesion in the FEF region were particular in that they showed an increased percentage of express saccades in the gap-random condition, the effect being especially prominent with ipsiversive saccades. On the other hand, express saccades were largely suppressed in these patients, similar to normals, if fixation was not interrupted prior to target appearance as in the overlap-random condition.

Parietal lesions

The inter-condition differences in the group of parietal patients in whom the lesion spared the dorsolateral parietal cortex (i.e. those with parieto-medial and pericentral lesions) were similar to those of the normal controls. In the dorsolateral parietal patients, in contrast, the inter-condition differences were considerably reduced, especially with contralateral saccades. This result was mainly due to both a rare occurrence of express saccades with the gap-random condition and of anticipatory saccades with the gap-simultaneous condition. There was also an increase of time errors and an enlarged SRT scatter as reflected in the standard deviations.

Examples of SRT distributions from three parietal patients are shown in Fig. 4E–G. The SRT distributions of the patient with the parieto-medial lesion (Fig. 4G) are clearly structured and closely resemble those of the pericentral patient (Fig. 4E) and those of the control subject (Fig. 4A). The distributions of the patient with the dorsolateral lesion (Fig. 4E), in contrast, appear to be 'decomposed' with an almost random scatter of the SRT values over time, especially prominent with the simultaneous conditions and contralateral saccades. Note, that especially the number of contralateral saccades in the distributions are reduced. This reflects the high number of direction errors; in the overlap-simultaneous condition, for instance, this patient made 73% direction errors with contralateral saccades.

The results of the inter-group comparisons are shown in Fig. 6A–D. (i) With the gap-random condition, the dorsolateral parietal patients showed lower percentages of

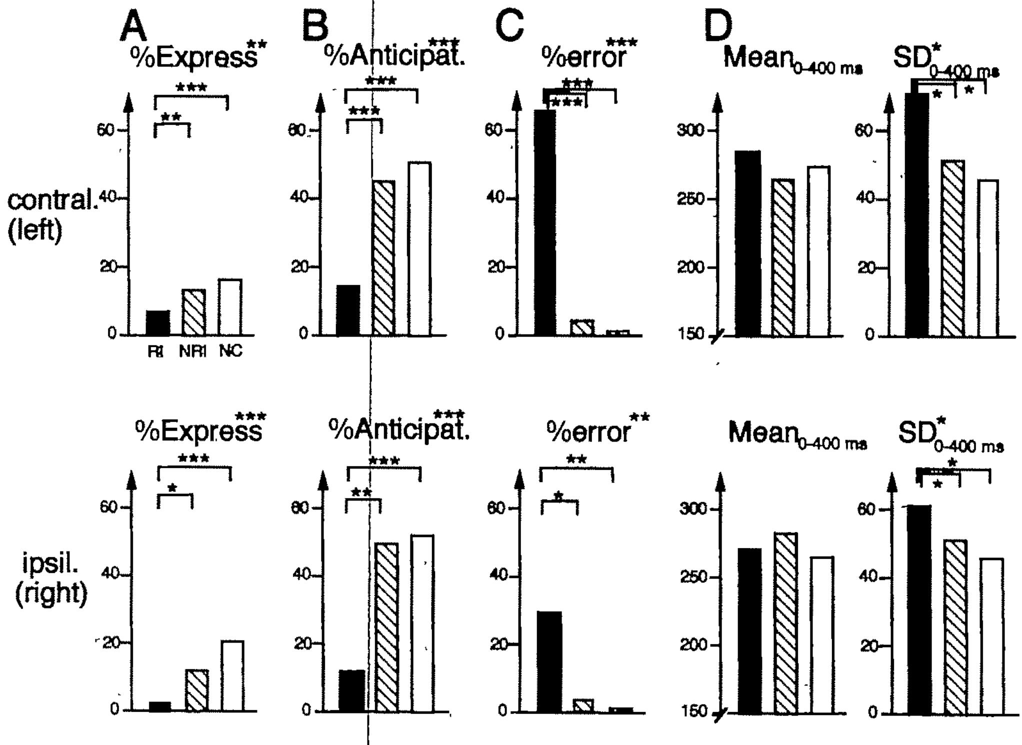

FIG. 6. Main statistical results of the parietal patients. RI, the patients with dorsolateral parietal lesion; NRI, the patients with pericentral and parieto-medial lesions. Otherwise presentation as in Fig. 5.

express saccades than the other patient groups and the normal controls both for the ipsilateral (χ^2: 13.61) and the contralateral (9.46) direction. (ii) With the gap-simultaneous condition, the dorsolateral parietal patients showed lower percentages of anticipatory saccades than the other two groups both for the ipsilateral (χ^2: 13.06) and the contralateral (16.01) direction. (iii) With the overlap-simultaneous condition, their percentages of direction and time errors were increased for ipsilateral (χ^2: 10.36) and more pronounced, for contralateral (22.7) saccades (the same applied to the other three stimulus conditions). (iv) The $M_{0-400\ \mathrm{ms}}$ values for the overlap-random condition were similar in all three groups, whereas the $SD_{0-400\ \mathrm{ms}}$ values were significantly higher in the dorsolateral parietal patients. Thus, remarkably, the most commonly used condition (one target, no gap) and the most commonly evaluated response parameter (mean SRT) in this kind of experiment did not reveal the impairment of the dorsolateral parietal patients in our study.

The grand average SRT distributions of five patients, in whom the lesion was essentially restricted to the dorsolateral parietal region, are shown in Fig. 7D. The decomposition of the SRT distributions is bilateral with a clear contralateral preponderance. Note the increased scatter when moving from the gap-random to the overlap-simultaneous condition. In other words, the impairment was relatively mild with the presentation of a single stimulus after fixation point offset (gap-random condition; no stimulus 'rivalry') and got stronger when immediately prior to saccade onset either the stimulus and the fixation point (overlap-random) or two stimuli (gap-simultaneous) were visible, and was strongest with two stimuli and the fixation point (overlap-simultaneous).

In the dorsolateral parietal patients, no statistical comparison across right (n = 6) versus left (n = 2) hemispheric lesions was possible. However, we can state that the percentages of direction errors for contralateral saccades in the overlap-simultaneous task of the two patients with a left hemispheric lesion (16% and 73%, respectively) was similar to that of patients with a right hemispheric lesion (12–72%) and that they were independent of the side of the lesion clearly larger than in normal controls (<3%). We therefore assume that the main findings apply to both right and left hemispheric lesions in the dorsolateral parietal cortex.

Taken together, the patients with a dorsolateral parietal lesion showed decomposed SRT patterns in that SRT variability was high and the percentages of time and direction errors were increased, especially if more than one stimulus was visible beside the saccadic target. This decomposition had a contralateral preponderance.

Comparisons across regions of interest

The inter-group comparison comprised the FEF patients, the patients with dorsolateral parietal lesion and the normal controls. With the gap-random condition, the percentage of express saccades was decreased in the dorsolateral parietal patients and increased in the FEF patients as compared with the normal controls. Anticipatory saccades in the gap-simultaneous condition were decreased in both patient groups, in the dorsolateral parietal patients more than in the FEF patients. In the overlap-simultaneous conditions (and the other three conditions), time and direction errors as well as SRT variability (SD values) were higher in the dorsolateral parietal patients than in the FEF patients and the normal controls.

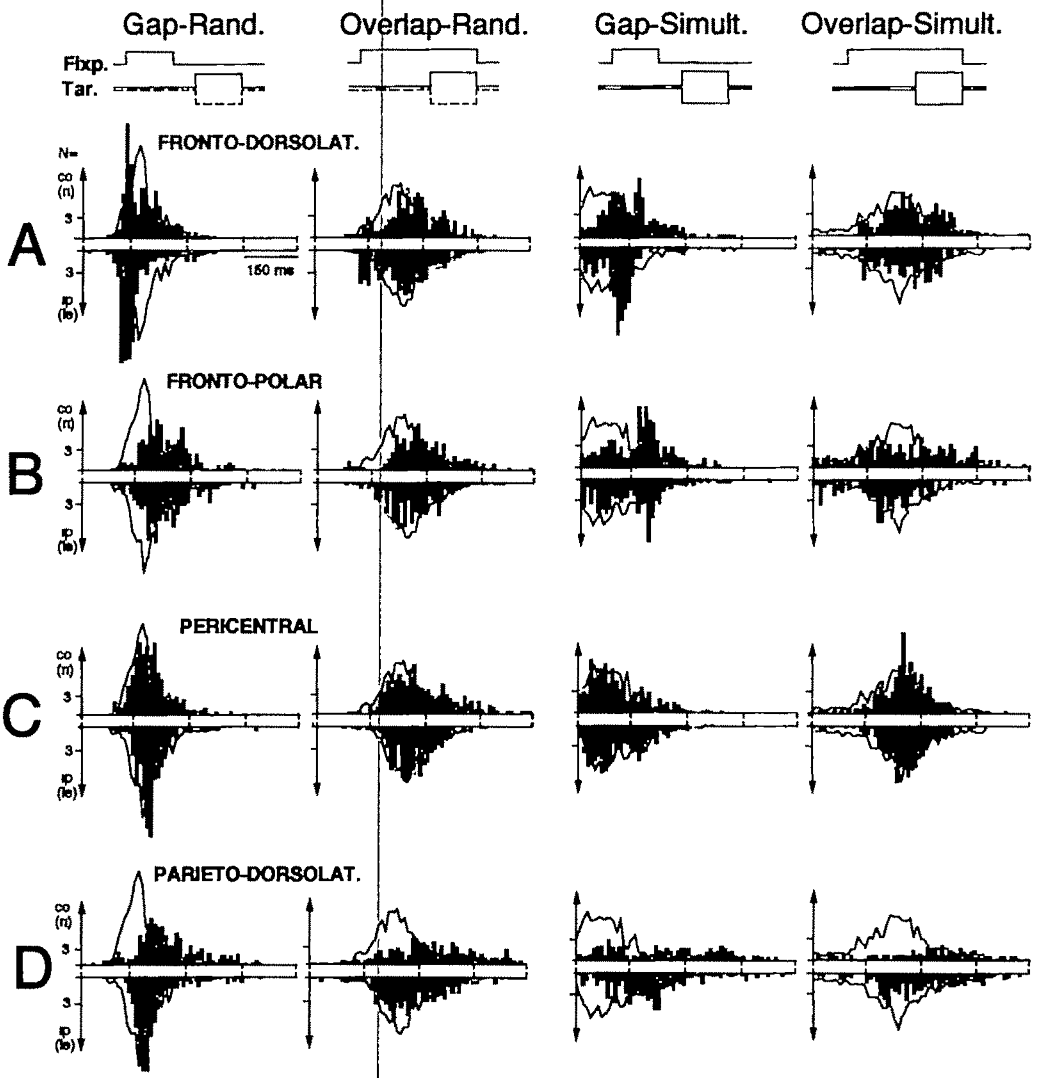

FIG. 7. Grand average SRT distributions of patients with a lesion in the fronto-dorsolateral region (A, FEF region), fronto-polar/basal region (B), pericentral region (C), and parieto-dorsolateral region (D). Only those patients were selected in whom the lesion was restricted to the indicated region For comparison, the outline of the SRT distribution of the control subjects is given as black or white curves superimposed on the SRT histograms Presentation as in Fig 4.

DISCUSSION

We investigated in humans the effect of subacute or chronic unilateral frontal and parietal lesions upon SRTs. Of special interest were lesions in the FEF and the dorsolateral parietal cortex, areas known to be involved in the generation of voluntary saccades. We found that mean SRTs (SRT <400 ms), with only a few exceptions, did not differ significantly across our frontal or parietal patient groups. More informative results were obtained by examining the distributions of SRTs under different stimulus conditions. In the following, we shall discuss the effects of lesions on the percentage of express saccades under gap and overlap conditions, the generation of anticipatory saccades towards a predesignated target location and the selection of the saccadic target among several, simultaneously presented visual stimuli.

Express saccades

A major goal of our study was to determine whether FEF lesions have a major effect on the occurrence of express saccades. Guitton *et al.* (1985) have shown that patients with frontal lesions in the area of the FEF had long-term difficulties to suppress reflex-like saccades to suddenly appearing visual stimuli in the anti-saccade task. These unwanted visually triggered saccades had very short SRTs in the range of express saccades. In healthy subjects attentive fixation at the time of target appearance prevents express saccades (Fischer and Ramsperger, 1984, 1986; Mayfrank *et al.*, 1986). We therefore asked whether fixation has the same suppressive effect on short-SRT saccades in FEF patients as in normal subjects? To answer this question we compared the SRTs of patients with frontal lesions within or outside the FEF region and control subjects under gap- and overlap-random conditions. This comparison revealed that with the gap-random task the percentage of express saccades was significantly increased in all frontal patients and control subjects. However, FEF patients showed a much higher percentage of contraversive and, even more pronounced, ipsiversive saccades with SRTs in the express range than the other subject groups. The significant increase of express saccades found only with FEF patients indicates that lesions of the FEF have a major influence on the occurrence of short-SRT saccades.

The high percentages of short-SRT saccades of our FEF patients led to a decreased value of the mean SRT in the gap-random condition. This result may possibly be related to that of Pierrot-Deseilligny *et al.* (1987), who measured the mean SRT in patients with unilateral frontal lesions under conditions in which the gap duration was randomized. Out of 13 patients, seven showed a directional asymmetry with remarkably short mean SRTs for ipsiversive saccades, while two patients showed short mean SRTs bilaterally.

There is an apparent discrepancy between our results and those of Schiller *et al.* (1987), who found that the percentage of express saccades in monkeys is similar before and after FEF lesion. However, these authors extensively trained their monkeys before testing, and training increases the frequency of occurrence of express saccades up to some maximal level in both monkey (B. Fischer, personal communication) and man (Fischer and Ramsperger, 1986). We therefore assume that after FEF lesions Schiller *et al.* (1987) observed no major change in the percentage of express saccades in their monkeys since the preoperative value in these animals was already close to its maximum. In contrast, the patients in the present study had not been trained before testing.

Another goal was to study the effect of attentive fixation upon the elicitation of short-SRT saccades. The percentage of express saccades was reduced by a factor of 6 in the overlap-random compared with the gap-random condition in our normal subjects. Similar figures were obtained in the frontal patients including those with FEF lesions. The suppressive effect of fixation was also found in an additional patient with *bilateral* frontal damage of the white matter following carbon monoxide intoxication. The SRT distributions for the gap- and overlap-random conditions of this patient are shown in Fig. 8. In this patient, who showed the highest percentage of express saccades in the gap-random condition that we have obtained in an untrained adult subject, the percentage of express saccades was reduced by a factor of ≈ 10 in the overlap-random condition. This result indicates that suppression of short-SRT saccades by attentive fixation is not affected by FEF lesions.

In the study of Guitton *et al.* (1985), the appearance of the peripheral saccadic cue coincided with the extinction of the fixation point. This might explain why their FEF patients produced a high percentage of visually triggered, short-SRT saccades in both of their tasks (compare mean SRTs of their FEF patients, Table 2). Different from Guitton *et al.* (1985), our results indicate that the occurrence of express or reflex-like saccades is highly dependent on the state of fixation and not whether saccades were to be initiated in the direction of (pro-saccade task) or in the direction opposite (anti-saccade task) a visual stimulus.

Schiller *et al.* (1987) showed that the generation of express saccades depends on the integrity of the superior colliculus (SC). Ablation of either the FEF or the SC does not abolish permanently voluntary saccades, whereas a combined lesion of both structures produces such a pronounced impairment (Schiller *et al.*, 1980, 1987). Thus, two parallel pathways seem to exist for saccadic control, one pathway that includes the FEF and appears to exert an inhibitory control upon the SC and another pathway via the SC, which appears to be independent of the FEF. Several projections from the FEF region to the SC have been described in anatomical (Leichnetz *et al.*, 1984) as well as in neurophysiological studies (Hikosaka and Wurtz, 1983; Wurtz and Hikosaka, 1986; Segraves and Goldberg, 1987), but it is so far unclear which of these pathways would be responsible, on disruption, for a release of express saccades with an ipsilateral preponderance as observed in our FEF patients. At this point, we have to emphasize that the frontal regions of interest certainly extend beyond the FEF described by recent studies on regional cerebral blood flow in humans (Fox *et al.*, 1985). Therefore, we cannot exclude completely that structures adjacent to the FEF may exert inhibitory control on the SC and thus prevent the elicitation of inappropriate reflex-like saccades.

Different studies have shown that visual attention has a strong effect upon SRTs (Mayfrank *et al.*, 1986; Fischer and Breitmeyer, 1987; Braun and Breitmeyer, 1988).

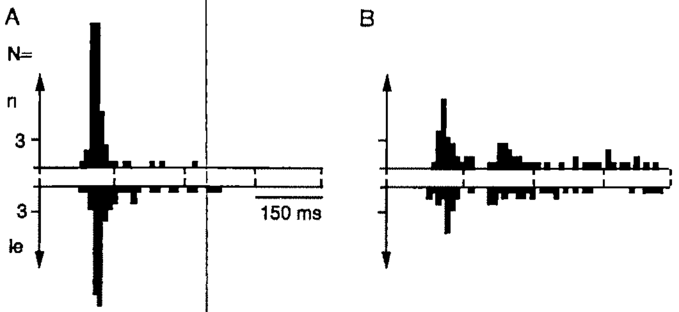

FIG. 8. Saccadic reaction time distributions of an additional patient with bilateral lesion of the frontal white matter Note the marked suppression of express saccades in the overlap-random (B) as compared with the gap-random (A) condition.

According to these authors, the occurrence of express saccades in normals depends on a disengaged state of visual attention which is favoured under gap conditions. Furthermore, under overlap conditions, disengaging attention from the fixation point requires an additional time-consuming step in saccade preparation and consequently shifts SRTs towards that of regular saccades. Posner *et al.* (1984, 1987) proposed that the (right) posterior parietal lobe has a specific role in attention processing, i.e. to disengage directed visual attention from its current locus. This hypothesis was based on the observation that patients with right parietal lesions showed significantly slower manual reaction times to contralateral stimuli following invalid spatial cues.

Previous work has shown that unilateral lesions of the posterior parietal cortex also produce disorders of saccadic eye movements. In patients with right parietal lesions, Sundqvist (1979) and Nagel-Leiby *et al.* (1990) found increased SRTs to contralateral stimuli. A bilateral increase of both mean SRTs and standard deviations has recently been reported by Pierrot-Deseilligny *et al.* (1987) for patients with left and right unilateral posterior parietal lesions tested with a gap task. In monkeys with unilateral parieto-occipital lesions, a significant increase in mean SRT and standard deviation was found for saccades into the contralateral hemifield, while saccade accuracy was not or only slightly affected (Lynch and McLaren, 1989).

If posterior parietal lesions produce a deficit in attentional disengagement, then the different states of directed visual attention as in the gap- and the overlap-random task should be reflected in pronounced SRT differences when SRTs of parietal patients tested under both conditions are compared. For example, under gap-random conditions patients with (right) dorsolateral parietal lesion might show a normal SRT distribution, since attentional disengagement from the fixation point is facilitated by its extinction and can be completed during the gap, while under overlap-random conditions SRTs of contraversive saccades might be increased.

However, the SRT distribution of all patients with dorsolateral parietal lesions showed bilateral deficits under both conditions. In the gap-random condition the percentages of express saccades to the ipsi- and the contralateral side were significantly reduced. Also under gap-random conditions the standard deviation was increased, but this deficit was more severe with the overlap-random task and with saccades to the contralateral side. Whereas the SRT distributions of control subjects and all other patients had distinct structures, the distributions of patients with dorsolateral parietal lesions were largely scattered over the whole spectrum of SRTs under both conditions. The increased standard deviations and the high percentage of time errors (SRT > 400 ms) might be caused by a destruction of stimulus-triggered saccade timing. No evidence for hemispherical differences was found, when we compared the SRT distributions of two patients with a left-sided lesion with those of patients with a right-sided lesion. In general, unilateral dorsolateral parietal lesions effected saccadic eye movements bilaterally but more pronounced in the contralateral direction while FEF lesions effected mainly ipsiversive saccades.

Anticipatory saccades

In this study we also pursued the hypothesis that the frontal cortex may be involved in the volitional initiation of saccades, such as anticipatory and memory-guided saccades.

According to Segraves and Goldberg (1987), the FEF is important for the generation of purposive saccades, because the oculomotor regions in the SC received distinct messages from FEF neurons about the state of fixation and the targeting information regarding intended saccades. This conclusion is based on the finding that half of the FEF neurons projecting to the SC show strong activity before both visually and memory-guided saccades. Also, anticipatory activity was found in FEF neurons, when the stimulus condition was kept constant over several trials (Bruce and Goldberg, 1985).

Neuronal response activity preceding saccadic eye movements was not only found in the FEF but also in the prefrontal (Boch and Goldberg, 1989; Funahashi *et al.* 1990) and in the dorso-medial frontal cortex. Schlag and Schlag-Rey (1987) showed that in the dorso-medial frontal cortex, rostral to the SMA, a small area exists, which may be specialized for self-initiated saccades. Whereas in the FEF a visual cue seems to be essential to obtain a presaccadic discharge (Bruce and Goldberg, 1985), in this 'supplementary eye field' (SEF) cortical unit activity was found before purposive as well as before spontaneous saccades in the dark.

Recent lesion studies in monkeys support the notion that the FEF mediates complex oculomotor behaviour such as memory-guided or predictive (anticipatory) saccades. Deng *et al.* (1986) found that after unilateral FEF lesions, monkeys had severe long-lasting impairments to perform accurate saccades to remembered target locations in the contralateral hemifield. The performance of visually guided saccades to targets in both hemifields was normal. Bruce and Borden (1986) studied eye movements of monkeys with bilateral FEF lesions with two square-wave motion tasks: in one task, the regularly moving target was always visible, while in the other, the gap square-wave task, the target disappeared for 250 ms before each step. After FEF ablation, monkeys were still able to precisely track the square-wave motion, but in the gap task the predictive saccadic tracking, which was found preoperatively, was no longer produced: anticipatory saccades had disappeared; however, saccades with SRTs in the express range were still present.

In our gap-simultaneous task, the stimulus was highly predictable: saccade direction was given by instruction, the location of the visual stimuli was kept constant and target appearance was announced by the preceding extinction of the fixation point. As a consequence, the percentage of anticipatory saccades was very high in normal subjects. In patients with frontal lesions, however, anticipatory saccades were reduced particularly to the contralateral side. The decrease was even more pronounced when the lesion was located in the FEF region or more anteriorly or medially. Interestingly, in the gap-simultaneous condition the FEF patients performed express rather than anticipatory saccades. We therefore conclude that frontal lesions affect anticipatory saccadic eye movements.

Since anticipatory saccades are intentionally triggered saccades to expected target locations, their reduction as found in our patients might be caused by an attenuation of related processes such as spatial coding or saccade initiation. Pierrot-Deseilligny *et al.* (1991) found that in patients with unilateral lesions of the dorsolateral frontal cortex memory-guided saccades in the contralateral and the ipsilateral directions had increased SRTs and errors in amplitude. These authors suggested that the preparation of memory-guided saccades may involve in addition to the FEF, two other frontal structures; i.e. area 46 for memorizing the target location and the SMA for saccade timing. From our results no such specific assignment was possible; the percentage of direction and time errors of the frontal patients was similar to those of our control subjects. Since this was also true for the FEF patients, one can assume that the selection of the target side was successfully determined prior to saccade initiation.

The percentage of anticipatory saccades in the gap-simultaneous condition was even more reduced in the patients with dorsolateral parietal lesion. This deficit was bilateral. We relate this finding not to a specific impairment of this saccade type, but rather consider it a secondary one, due to a deterioration of target selection and coding caused by dorsolateral parietal lesions.

Target selection

One characteristic syndrome, which might occur in humans after (right) posterior parietal lesions is inattention towards the contralateral body half and visual space (Brain, 1941; Roth, 1949; Critchley, 1953; DeRenzi, 1983; Heilman *et al.* 1985). In severe cases of attentional disorders, any sensory stimulus in the contralateral hemifield is ignored (contralateral neglect). After recovery and in less severe cases, attentional deficits to contralateral stimuli are mainly found when stimuli appear simultaneously and symmetrically in the two visual hemifields (visual extinction). Under these conditions patients are found to respond mainly to the stimulus in the ipsilateral hemifield (Denny-Brown *et al.*, 1952; Karpov *et al.*, 1968; Gainotti *et al.*, 1986; Weintraub and Mesulam, 1987).

Also in monkeys contralateral visual extinction was seen after unilateral posterior parietal or parieto-occipital lesions when two symmetrically located stimuli were presented at the same time (Lynch and McLaren, 1989). In electrophysiological recordings in trained monkeys, Bushnell *et al.* (1981) have found that neurons in parietal area 7a show increased activity when a visual stimulus was attended, regardless of whether it was a goal for a saccadic eye movement or not. These authors concluded that area 7a participates in directing of visual attention by providing an amplified signal to selected stimuli.

Given that a patient has an impairment of target selection, one could expect that he/she shows an increase of direction errors, depending on the number of visual stimuli that compete with the target stimulus. Across the four conditions used in our study, the number of simultaneously presented visual stimuli varied: after fixation point offset, one novel stimulus appeared in the gap-random task, the fixation point and one novel stimulus were present in the overlap-random task, two novel stimuli appeared in the gap-simultaneous task, the fixation point and two novel stimuli were present in the overlap-simultaneous task.

While no major impairment of target selection was found with frontal lesions, the patients with dorsolateral parietal lesion showed a high percentage of direction and time errors which increased with the number of simultaneously presented visual stimuli. In both the gap-simultaneous and the overlap-simultaneous condition time or direction errors occurred in half of the trials when saccades were to be initiated to the contralateral stimulus. Even when the patients were informed about their directional errors, they could not control the direction of their eye movements. Also the extinction of the fixation point as in the gap-simultaneous condition did not reduce the percentage of errors. These results indicate that after dorsolateral parietal lesions the knowledge of the target location and its appearance cannot be used efficiently. This notion is supported by the fact that memory-guided saccades of patients with posterior parietal lesions showed a significant increase in SRT and error in amplitude (Pierrot-Deseilligny *et al.* 1991).

Behavioural and clinical data have indicated that the posterior parietal cortex of primates has a crucial function in spatial perception and spatially oriented behaviour such as target-directed hand and eye movements (Luria *et al.*, 1963; Hyvärinen and Poranen, 1974; Mountcastle *et al.*, 1975; Robinson *et al.*, 1978; Girotti *et al.*, 1983; Andersen, 1989; Lynch and McLaren, 1989). Recent experiments in monkeys suggest that a functional segregation exists within the posterior parietal cortex. While area 7a appears to be important for spatial analysis through integration of eye position and retinotopic visual information, the lateral intraparietal area seems to be specialized for programming of intended saccadic eye movements (Andersen *et al.*, 1987, 1990). Gnadt and Andersen (1988) showed that neurons in the lateral intraparietal area have, besides visual, also memory-linked activity which was present when the monkey had to perform saccades to remembered spatial locations. According to the authors these neurons encode the amplitude and direction of intended saccades. Duhamel *et al.* (1992) found that neurons in this area seem to anticipate the retinal consequences of intended eye movements, because the location of their receptive field shifts transiently before saccades. This predictive shift allows, according to the authors, to re-map and update the internal representation of the visual space in advance of eye movements. The lateral intraparietal cortex might therefore be of special importance in the performance of saccades to known target locations initiated before (anticipatory saccades) or after (remembered saccades) target appearance.

The dorsolateral parietal cortex receives visual information from the visual cortex, and has reciprocal connections with the FEF (Pandya and Kuypers, 1969; Chavis and Pandya, 1976; Jacobson and Trojanowski, 1977; Barbas and Mesulam, 1981). In addition, projections from the posterior parietal cortex reach the SC directly (Petras, 1971; Lynch *et al.*, 1985). This anatomical arrangement makes the dorsolateral parietal cortex an important centre of visuo-motor integration, which may influence the saccadic oculomotor behaviour both via the frontal cortex as well as independently.

Taken together, the present study shows that subacute or chronic unilateral lesions in both the frontal and the dorsolateral parietal cortex may permanently impair volitional initiation and control of goal-directed saccades. The deficits caused by these lesions, however, seem to be different. When the frontal lesion included the FEF, volitional control of visually triggered, reflex-like saccades was disinhibited if fixation was disrupted prior to target appearance. In the gap-simultaneous condition, both groups of patients had difficulties initiating anticipatory saccades. In the patients with frontal lesions, mainly self-initiated saccades were impaired. In patients with dorsolateral parietal lesions SRT distributions of all conditions were largely decomposed. The increase of the percentage of direction and time errors with the number of simultaneously presented visual stimuli indicated that after posterior parietal lesions earlier steps of saccade preparation appeared to be impaired, i.e. the utilization of information about location and appearance of the target. Our study shows that the oculomotor deficits following unilateral lesions of the dorsolateral parietal cortex are clearly more severe than those resulting from frontal lesions.

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SACCADIC DYSMETRIA IN A PATIENT WITH A RIGHT FRONTOPARIETAL LESION

THE IMPORTANCE OF COROLLARY DISCHARGE FOR ACCURATE SPATIAL BEHAVIOUR

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SUMMARY

Double-step experiments have demonstrated that retinotopic coding is inadequate to explain the spatial performance of the saccadic system. In such experiments a subject is asked to make two successive saccades to fixate two sequentially flashed targets each of which disappears before the first saccade. Despite the dissonance thus created between the retinal location of the second target and the saccade necessary to acquire it, normal humans and monkeys perform the task perfectly well. Single unit recording in monkeys indicates that neurons in the superior colliculus, frontal eye fields and in parietal cortex generate a spatially accurate signal during the performance of double-step saccades, which is thought to be obtained by combining a retinotopic signal with a signal corollary to the previous saccadic eye movement.

We studied saccadic eye movements in a patient with a right fronto-parietal lesion using single- and double-step tasks. Single saccades into the left (contralesional) hemifield had longer latency and were hypometric relative to those into the right (ipsilesional) hemifield. Varying the initial orbital position had no effect on the latency and accuracy of saccades to left and right retinal stimuli. When the patient was asked to do a double-step task with targets flashed first into the right field and then into the left field, she performed well. When she was asked to do the same task with a target flashed first into the left field and then into the right field she made the first saccade correctly but never acquired the second target, even though this required her to make a saccade in the normal direction to a stimulus that appeared in the normal field. Such a deficit therefore cannot be one of retinotopic or spatial coding, nor can it be one of generating a certain direction of saccade. We suggest that the deficit is a failure of corollary discharge, the inability to register the amplitude and direction of a saccade into the contralesional field, and use that information to update the representation of the location of the next saccade target.

INTRODUCTION

One of the basic tasks that the brain performs is to coordinate information about the environment and information about the internal state of the organism. In the visual-oculomotor system, saccadic eye movements have long been recognized as a useful tool to study the interactions between retinal and extra-retinal signals in different brain regions (Goldberg and Wurtz, 1972; Bushnell *et al.*, 1981; Fischer and Boch, 1981). The question

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of the role of extra-retinal signals in eye movements addresses directly the broader issues of reference frames and spatial representation.

From a behavioural standpoint, it has been established that the processing taking place during saccadic eye movements requires both visual and non-visual signals. In a now classic experiment, Hallett and Lightstone (1976) devised an oculomotor task, the double-step paradigm, in which two consecutive saccades were made in response to two sequentially flashed visual targets (Fig. 1). Because the duration of the stimuli was very brief, the saccades were initiated and executed in darkness. Normal human subjects can perform this task quite accurately. This finding refutes the notion that only retinal information is available to the oculomotor system in planning an eye movement: since the second saccade does not start at the spatial location from which the second visual target was seen, the double-step task introduces a spatial dissonance between the retinal coordinates of the target and the motor coordinates of the required eye movement. In order to compensate for this and to compute an accurate saccade, non-retinal information about the displacement of the eye since the target was seen must therefore be used.

How this computation is accomplished remains a subject of debate. One position states that retinal and eye position data are added to produce a supra-retinal craniotopic representation of visual space (Mays and Sparks, 1980; Zipser and Andersen, 1988;

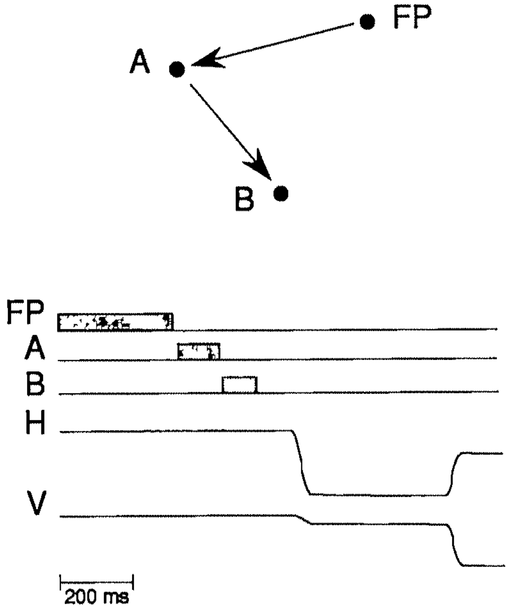


FIG 1 Double-step saccade experiment FP = fixation point, A and B, first and second saccade targets; H and V, horizontal and vertical eye position. The top part of the figure shows the location of the targets and the sequence of saccades. The bottom part shows the timing of visual and oculomotor events (time runs from left to right). Note that the targets were extinguished before any eye movement took place This created a dissonance between the retinal coordinates of the stimulus at B and the motor coordinates of the saccade to it: B was flashed in the left visual field but had to be acquired with a rightward eye movement.

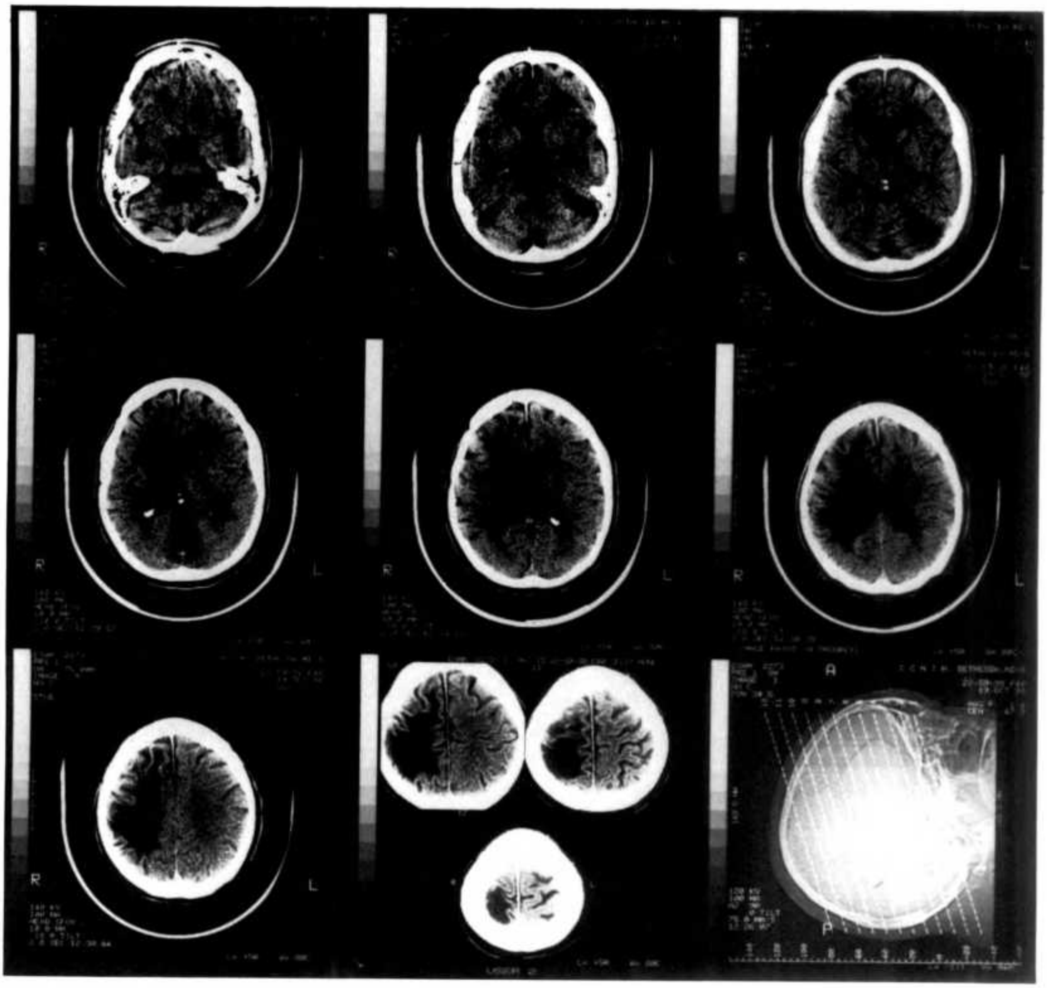


FIG. 3. Patient's CT scan showing large right hemispheric lesions (details in text).

data, the signals from the coil were calibrated by having the subject fixate spots of light located at the centre of the screen and 10° right, left, above and below this point. Experiments were carried out under computer control (PDP 11/73). Horizontal and vertical eye position and target position were sampled at either 250 Hz or 1000 Hz. The computer monitored fixation, determined the order in which trials were presented, controlled the position of the target, digitized analogue signals and stored the data.

Oculomotor tasks

Visually guided saccades. The subject fixated the stimulus located in the centre of the screen. After an unpredictable delay, the spot of light disappeared and reappeared pseudo-randomly at one of 12 locations on the horizontal meridian (2°, 4°, 6°, 8° in the left visual field; 2°, 4°, 6°, 8°, 10°, 12°, 14° in the right visual field). The subject's task was simply to make a saccade to the stimulus and maintain fixation at the new location until the end of the trial. Each target location was tested 8–10 times. The main purpose of this task was to measure the latency, amplitude and velocity of single saccades to targets in the left and right visual fields.

Visually guided saccades from multiple initial positions. The block of trials began with the subject fixating a target at the centre of the screen. At an unpredictable time after the onset of the fixation target, one of two targets located 5° to the left or to the right would appear and the subject would saccade to it. This target would provide the fixation point for the next trial, and the next target would appear pseudo-randomly 5° to the left or to the right. Therefore, although all saccades were of the same required amplitude and only differed in direction, their goal in head-centred space varied systematically as a function of initial eye position. Initial position ranged, in 5° steps, from 20° to the left to 20° to the right of primary position (which coincided with the centre of the screen). Eleven trials were collected for each direction of saccades from each initial eye position.

Double-step saccades. After an unpredictable delay from the onset of the fixation period, the central fixation stimulus disappeared and the first saccade target was flashed for 100 ms. This flash was immediately followed by a second saccade target which was flashed for 80 ms. The patient's task was to shift rapidly her gaze from the fixation to the first target location and from there to the second target location. Since the latency of the first saccade was longer than the total duration of the two stimuli, both saccades were made while the screen was blank. These two saccades can therefore be said to be visually triggered, but they are not visually guided. In this paradigm visual information about the second target is sampled prior to the beginning of the first eye movement. Unequal stimulus durations were used because previous experience with this paradigm has shown that this reduces the probability that a subject will make the saccades in the reverse order (from the fixation point to second target to first target) or make a single direct saccade to the second target.

Four different pairs of double-step target combinations were used. Two of the pairs consisted of stimuli appearing in the same visual hemifield and the two other pairs consisted of one stimulus in each visual hemifield. Further details about the location of the stimuli are given in Results. Each stimulus combination was presented 12 times in a series of randomly intermingled trials. A slowed-down version was also used as a control task for some of the target combinations, with each stimulus remaining on the screen for 500 ms. Since the latency of the first saccade was invariably less than 500 ms, this amounted to a sequence of two visually guided saccades. The spatial aspects of the slow and fast trials are identical, but the visual information available to the oculomotor system is different since in the slower case the second stimulus appears at the end of the first saccade.

Data analysis

Data analysis was performed off-line. Trials were examined for blinks and other disruptive artefacts, and for first-saccade latencies shorter than 180 ms in the double-step experiments; such trials were excluded. The computer differentiated each eye position record and used the resulting velocity record to search for saccades. The computer identified the time of onset and end of each saccade, and measured the eye and target positions at these times. Most saccades were horizontal but in the double-step experiments some saccades had a vertical component. The analysis program detected the beginning and end of the vertical component of the (oblique) saccade, and then measured the horizontal component during this period. We assured ourselves, by visual inspection, that the horizontal component of the saccade occurred within the timing of the vertical component, so that our measure of the horizontal component was indeed accurate. Data reported in the tables are only for the horizontal components of those saccades.

RESULTS

Visually guided saccades: effect of retinal location

Sample eye movement traces for all stimulus eccentricities are shown in Fig. 4 and averaged data for each set of trials are presented in Table 1. For both leftward and rightward saccades, large eye movements were associated with longer latencies than small eye movements. However, saccades to stimuli in the contralesional visual field had markedly increased initiation latencies relative to symmetrical locations in the ipsilesional visual field. The mean latency difference between leftward and rightward eye movements is about 78 ms. The left-right differences are significant for all symmetrical target pairs ($P < 0.01$ or less). Data reported elsewhere on the same patient

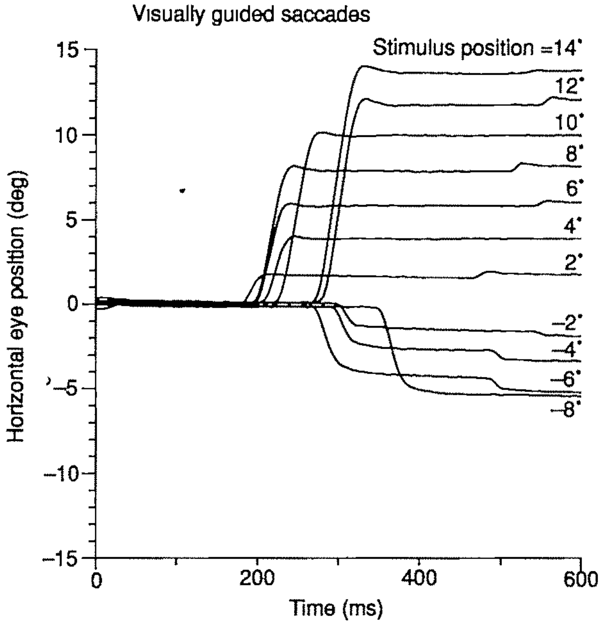


FIG. 4. Sample horizontal eye traces for saccades to left (−) and right (+) visual field targets. The saccade target remained visible throughout the trial.

TABLE 1 AMPLITUDE AND LATENCY OF VISUALLY GUIDED SACCADES TO RIGHT (+) AND LEFT (−) VISUAL FIELD STIMULI

Stimulus location (degrees)	*Latency (ms) mean (SD)*	*Amplitude (degrees) mean (SD)*	*Percentage undershoot*
14	362 (117)	13.5 (0.6)	3
12	300 (82)	11.5 (0.4)	4
10	242 (50)	9.7 (0.5)	3
8	242 (72)	7.6 (0.6)	5
6	216 (21)	5.7 (0.3)	5
4	219 (16)	4.0 (0.3)	0
2	213 (28)	1.8 (0.1)	10
−2	305 (13)	−1.6 (0.5)	20
−4	303 (16)	−2.3 (0.3)	42
−6	289 (8)	−4.0 (0.4)	32
−8	363	−4.8	40

indicate that the increased saccade latencies may in part be due to attentional factors (Duhamel *et al.*, 1990) though other variables such as increased delays in visuo-spatial analysis and/or response programming could play a role as well. There was no convincing evidence for blindsight. The patient made saccades into the seeing field, but almost never beyond the border of the scotoma. She did make one extremely hypometric saccade to a target 8° into the contralesional field, which is reported in Table 1 without a standard deviation.

Saccades to contralesional stimuli undershot their target by an average of 34% of the required movement amplitude. Thus undershoot ranged from 20% to 42% depending on target eccentricity but the amount of undershoot was not related in any systematic way to saccade amplitude. Saccades to ipsilesional targets had near perfect accuracy, with a mean undershoot of only 4% with a range between 0% and 10%, again without any clear relationship between amount of undershoot and saccade amplitude. The left-right differences were significant for all symmetrical target pairs ($P < 0.001$) except at 2°, by Student's t test. The amplitude/velocity profile of eye movements was similar for eye movements in the two visual hemifields (Fig. 5), indicating that the dysmetria of leftward saccades was not associated with abnormal saccade dynamics (Becker, 1989).

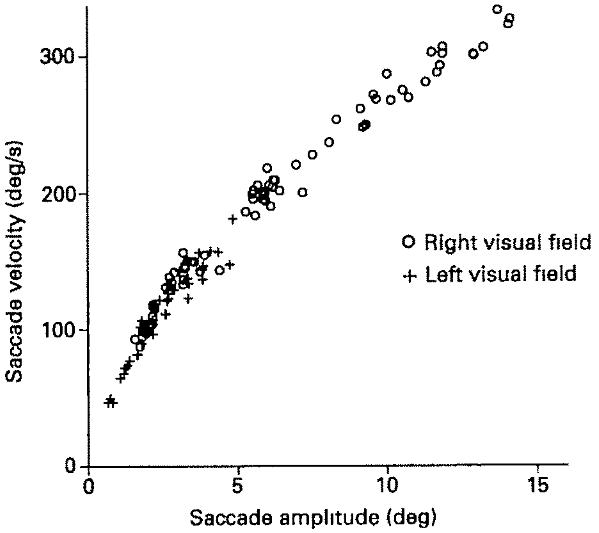


FIG 5 Velocity of eye movements as a function of their amplitude for visually guided saccades.

Visually guided saccades: effects of orbital position

In order to determine the influence of the craniotopic spatial location of a visual stimulus on eye movements, the initial orbital position of the fixation stimulus was varied from 20° left to 20° right of primary position. The saccade targets were always presented at one of two possible retinal locations: 5° to the left or to the right of the fixation point. Analysis of variance revealed a strong effect of the stimulus' retinal location on both saccade latency and amplitude but there was no significant effect of angle of gaze (Fig. 6). Saccades had longer latencies and shorter amplitudes for left than right visual field targets (both $P < 0.0001$) at all spatial locations, consistent with the results reported above. An unexpected influence of orbital position on saccade velocity was found, however, in an interaction between angle of gaze and saccade direction ($P < 0.005$). The velocity of leftward saccades was consistently slower than that of rightward saccades as shown in Fig. 6, in keeping with their smaller amplitude. In addition, for leftward saccades

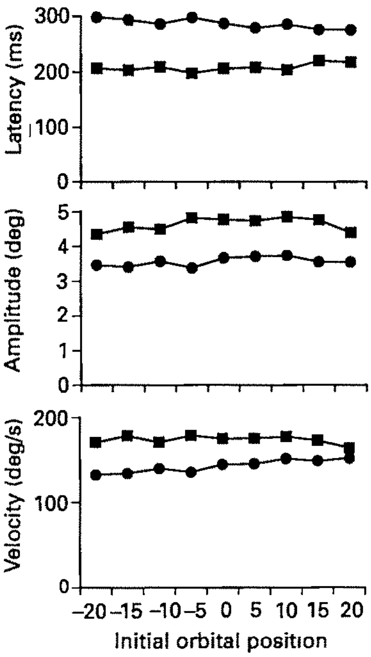


FIG. 6. Latency, amplitude and velocity of saccades to left (●) and right (■) 5° horizontal targets made from initial orbital positions ranging from 20° to the left to 20° to the right of primary position.

only, *a posteriori* contrasts revealed a linear trend toward a decrease in velocity as the fixation target moved from the right to the left of the orbit. However, this effect was modest, as a regression analysis showed that orbital position accounted for only 19% of the total variance in the velocity of these saccades.

In conclusion, it appears that saccades to left visual field targets were harder to initiate and less accurate than saccades to right visual field targets and mostly independent of orbital position.

Double-step saccades

Two stimuli in the same visual field: effect of stimulus location. These pairs of double-step stimuli were used to determine whether the inaccuracy of E.C.'s saccades was related to the retinal location of the targets (left versus right visual hemifield) or to the direction of the eye movements (leftward versus rightward saccades). Two stimuli were presented in rapid succession in the same hemifield, and the patient was required to saccade first to the most eccentric stimulus, and then back to the most central stimulus. For example, as illustrated in the top part of Fig. 7, sequence B, a stimulus was flashed for 100 ms at 6° right and 1.5° down and then for 80 ms at 2° right and 1.5° down. The patient had to execute a rightward saccade to the first stimulus location, and then a leftward saccade to the second stimulus location. The critical aspect of this experiment is the timing of the visual events: both stimuli went on and off before the beginning of the first saccade. This manipulation allowed us to measure an eye movement in the

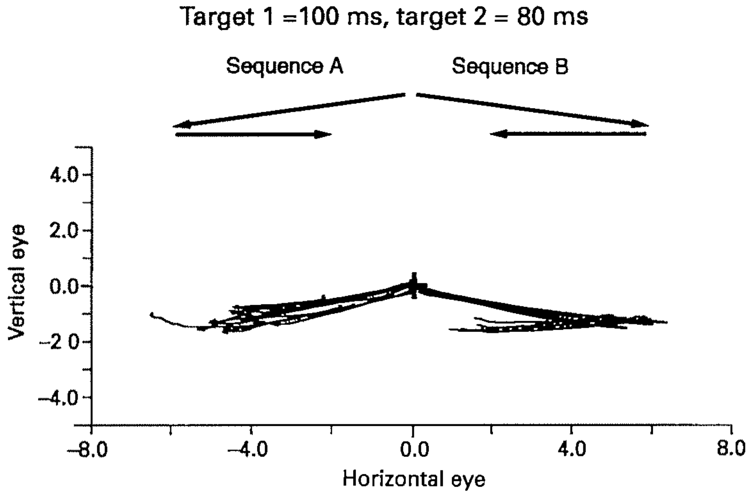


FIG. 7. Superimposed x-y plots of double-step saccades to a pair of left visual field stimuli and to a pair of right visual field stimuli. Stimuli were extinguished prior to the beginning of the first saccade. Arrows above the eye movement traces illustrate the two combinations of target steps.

contraversive direction with respect to the lesional hemisphere, but in response to a visual stimulus presented in the normal hemifield. As a control condition, the reverse pattern (sequence A), a rightward saccade to a left visual field target, was also tested by flashing the stimuli at the symmetrical locations to the left of the fovea. If the unilateral impairment observed in visually guided single-step saccades is determined by visual factors alone, saccades to left visual field targets (A) in the double-step task should be inaccurate, and saccades to right visual field targets (B) should be accurate, regardless of their direction. If the saccadic impairment is directional in nature, all leftward saccades should be inaccurate, including those made in the right visual field.

The results show that in the right visual field (ipsilesional, condition B), the first saccades had normal latency and accuracy, while in the left visual field (contralesional, condition A), the first saccades had increased latency and reduced amplitude, respectively $P < 0.01$ and $P < 0.02$ (Fig. 7, Table 2). This was expected from our earlier observations, since the first saccade in this task is analogous to a direct single step saccade, where the required movement amplitude matches exactly the retinal distance of the target

TABLE 2 SACCADE AMPLITUDE AND LATENCY OF E C IN THE DOUBLE-STEP EXPERIMENTS WITH TWO STIMULI IN THE SAME VISUAL HEMIFIELD

Step order	*Right* ⟶	*Left*	*Left* ⟶	*Right*
Step duration	100	80	100	80
Stimulus eccentricity	6	2	−6	−2
Required saccade amplitude	6	−4	−6	4
Actual saccade amplitude (degrees)	5.3 (0.4)	−3.5 (0.9)	−3.8 (1 1)	0.9 (3.0)
Saccade latency (ms)	199 (20)	144 (30)	299 (36)	426 (153)

Standard deviations are given in brackets from the fovea. More critical is the second saccade of the double-step pair. Interestingly, leftward saccades to the 2° right visual field target (B) were initiated with a very short latency and were quite accurate. In contrast, rightward saccades to the left visual target (A) had long latencies, or were not executed at all, and never reached the target. The accuracy of leftward saccades made in response to a right visual field target thus rules out the hypothesis of a directional saccadic impairment and appears to be consistent with a retinotopic impairment. The marked inaccuracy of rightward movements in the left visual field condition (A), however, requires further considerations that are addressed below.

One stimulus in each visual hemifield: effect of saccade direction. The above results confirm the contribution of stimulus location to the performance of double-step saccades. As described in the Introduction, in this paradigm, while the retinal location of the first target uniquely determines the dimensions of the first saccade, the retinal vector of the second stimulus and the dimensions of the second saccade are not equivalent. Accurate coding of the latter requires a compensation for the displacement of the eyes associated with the first saccade. As suggested previously, this is only possible if there exists a stabilized representation of the stimulus with respect to the head, or if the visual system can update the gaze-centred representation of the location where the stimulus was flashed in conjunction with the first eye movement. Either solution necessitates a computation that combines the retinal coordinates of the stimulus and extra-retinal information about the eye (static eye position or corollary discharge signal).

To study this computation further, we had the patient make two opposite pairs of saccades to the same physical locations. By keeping the retinal information constant, the only variable is the required order of saccade directions; right-left or left-right. We used symmetrical locations at 3° out and 1.5° down in each visual hemifield, and the same stimulus exposure times as above for the first and second stimuli. The direction of the first and second saccade was determined by the order of appearance of the two stimuli. For example, when the stimulus sequence was right-left, the patient attempted to make a rightward saccade to the right visual field target followed by a leftward saccade to the left visual field target. Latency and accuracy of these eye movements were compared with that of the same saccades made in the context of a slow version of the double-step task. In the slow version, the two stimuli were presented for 500 ms, leaving ample time for the patient to execute the first saccade before the onset of the second stimulus. This slow version involved the same eye movements as the fast version, but the motor coordinates of both the first and second saccades were congruent with the visual coordinates of their respective targets. Since one of the two stimuli was presented in the left (contralesional) visual field, none of the double-step pairs were expected to be perfectly accurate. We expected the left saccades in both the left-right and right-left pairs to be hypometric. However, if the damaged cortical regions of the right hemisphere play a role in generating or channelling extra-retinal information associated with leftward eye movements, we might expect increased latencies and inaccuracy of the rightward movement which follows it as well.

The results for the slow version of the double-step task indicate latencies and amplitudes that are consistent with results obtained with visually guided single step saccades: leftward, contraversive saccades were hypometric ($P < 0.01$) and their latencies were longer than those of rightward, ipsiversive saccades ($P < 0.02$), regardless of saccade order

(Fig. 8 top two panels, Table 3A). In the fast version, the critical question is the accuracy of the second saccade and its capacity to reach the spatial location of a target whose retinal coordinates do not match the required saccade vector (Fig. 8 bottom two panels, Table 3B) In the right-left condition, the eye movement required to reach a target which appeared at 3° left and 1.5° down was a straight 6° leftward saccades. The actual saccades made by the patient had a mean latency of 196 ms and a mean amplitude of −4.8°. Since it followed a nearly perfectly accurate first saccade, the second eye movement undershot the target by about 20%. In the left-right condition, the results were strikingly different. In two out of 10 trials, the patient performed the saccades in the wrong sequence, going from the second target to the first target, and on other trials she made two consecutive leftward eye movements. These trials were excluded from quantitative analysis. For the remaining trials, the mean latency of the second saccade was 337 ms (SD = ±177), much longer than the corresponding rightward saccades in the slow version of the double-step task ($P < 0.01$). These saccades were also inaccurate, with a mean amplitude of 2.2°. In most csaes it was impossible to determine whether the second saccades were actually directed at the second target or were simply return saccades to the fixation location.

In conclusion, in response to identical retinal stimuli, the patient made very different eye movements depending on the sequence that she had to follow. While she performed right-left combinations with adequate latency and accuracy, rightward movements in the left-right combination were markedly impaired. This occurred only for brief target presentations which created a spatial mismatch between the retinal input and the required motor output.

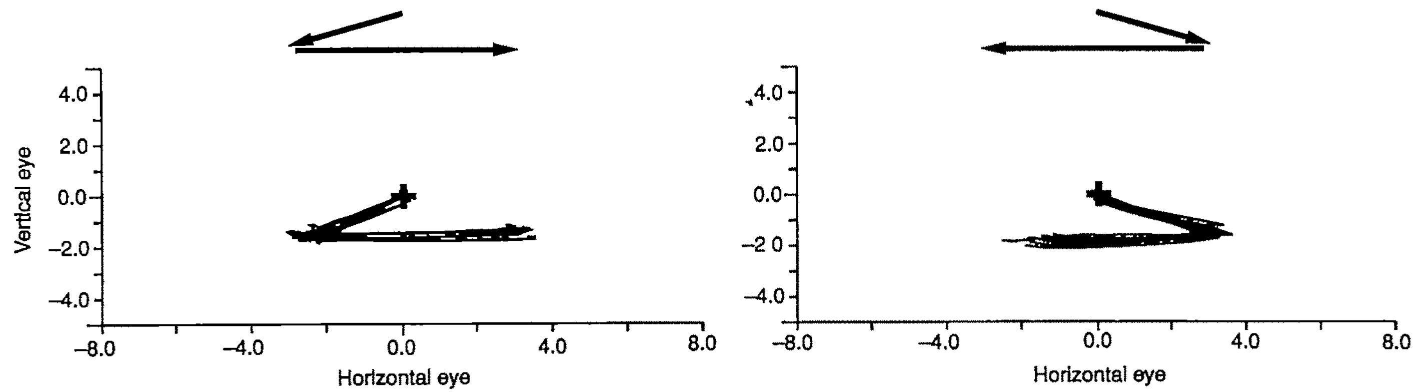
DISCUSSION

The patient described in this report had two sorts of deficits: (i) an increase in latency and reduced amplitude for visually guided saccades into the contralesional hemifield, and (ii) a marked deficit in compensating for prior contralesionally directed saccades when she was asked to make sequences of saccades to briefly flashed targets. She had no consistent deficit for saccades to a particular location in cranio- or egocentric space. We will discuss these deficits in terms of current concepts of the saccadic system and the analysis of space by the cerebral cortex.

Retinal factors

Saccades made into the contralesional field were hypometric and had a slight increase in latency. This deficit was relatively independent of the orbital position from which the saccade was initiated. Saccadic impairments can be explained by either sensory or motor factors. Three findings rule out a motor intepretation of this deficit: (i) all saccades, both normal ipsilesional and hypometric contralesional ones, lay on the main sequence velocity-amplitude curve that defines normal saccadic performance (Bahill *et al.*, 1975; Becker, 1989); (ii) the hypometria increased with increasing target eccentricity in a non-linear fashion, so the deficit was not a simple decrease in saccadic gain; (iii) the double-step experiments showed that the patient could make perfectly accurate saccades in the contralesional direction when the targets that evoked those saccades were in the ipsilesional retinal field.

Target 1 = 500 ms, target 2 = 500 ms



Target 1 = 100 ms, target 2 = 80 ms

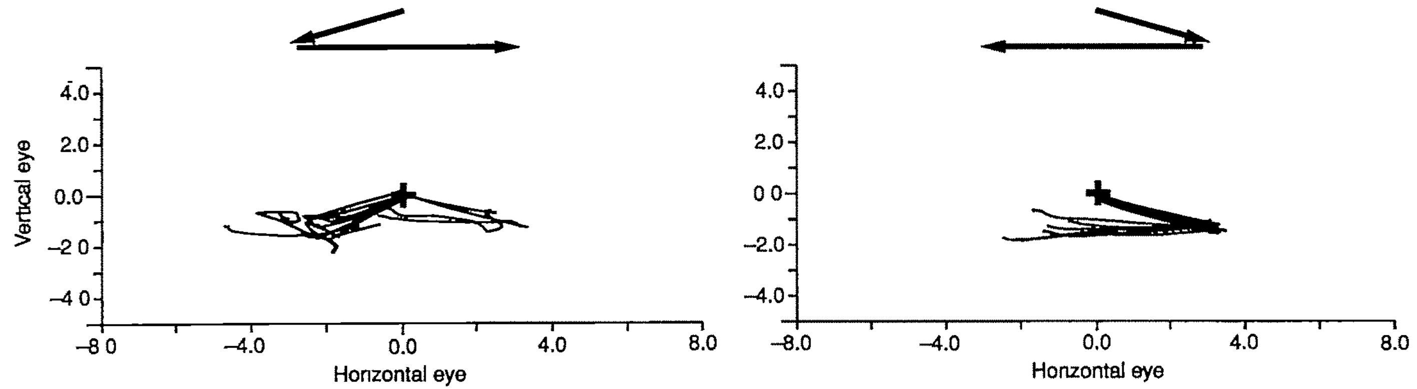


FIG. 8. Superimposed x-y plots of double-step saccades to pairs of left and right stimuli. Two different sequences of saccades were determined by the order of appearance of the stimuli, as indicated by the arrows above each plot. In the top two panels there is no dissonance between retinal and saccade vectors because the saccades were executed while their respective targets were visible. In the bottom two panels, retinal and saccade vectors for the second step are unequal because the second target was extinguished before the first saccade was initiated.

TABLE 3 SACCADE AMPLITUDE AND LATENCY OF E.C. IN THE DOUBLE-STEP EXPERIMENTS WITH ONE STIMULUS IN EACH VISUAL HEMIFIELD

Step order	*Right* →	*Left*	*Left* →	*Right*
(A) Two visually guided saccades				
Step duration (ms)	500	500	500	500
Stimulus eccentricity (degrees)	3	−6	−3	6
Required saccade amplitude (degrees)	3	−6	−3	6
Actual saccade amplitude (degrees)	3.1 (0.3)	−4.5 (0.7)	−2.2 (0.6)	5.8 (0.5)
Saccade latency (ms)	190 (36)	218 (33)	288 (30)	162 (177)
(B) Two visually-triggered saccades				
Step duration (ms)	100	80	100	80
Stimulus eccentricity (degrees)	3	−3	−3	3
Required saccade amplitude (degrees)	3	−6	−3	6
Actual saccade amplitude (degrees)	3.0 (0.3)	−4.8 (1.2)	−2.4 (0.6)	2.2 (2.6)
Saccade latency (ms)	186 (9)	196 (36)	363 (104)	337 (177)

Standard deviations are given in brackets.

It is not clear why a target in the contralesional retinal field should evoke a well-made hypometric saccade. One possible explanation is in terms of a distortion of the cortical input to the superior colliculus. Lee *et al.* (1988) demonstrated the importance of the active ensemble in the colliculus for the control of saccadic amplitude. They made small lesions in the retinotopic map in the intermediate layers of the superior colliculus. Saccades made to the centre of the collicular scotoma were accurate but slow. Saccades made to the near side of the scotoma were hypometric, and those made to the far side of the scotoma hypermetric. Because of our patient's hemianopia, it is reasonable to suggest that visual activity in the lesioned hemisphere is skewed toward the centre of the visual field. Since both parietal and frontal cortex project to the superior colliculus (Lynch *et al.*, 1985; Stanton *et al.*, 1988), the corticotectal projection in this case must excite a collicular ensemble also weighted toward the centre of the visual field, resulting in hypometria. The relative mildness of the deficit may be due to its chronic nature, which had allowed a significant adaptation to the effects of the lesion over the years.

Spatial factors

Cortical deficits have been classified as having a combination of hemifield and hemispace aspects (Heilman, 1979; Ladavas, 1987; Farah *et al.*, 1990). In a hemispatial deficit the patient has difficulty with targets lying in a particular region of space relative to an egocentric coordinate frame, regardless of the target's location on the retina. In a hemifield deficit the patient has difficulty with a certain area of the retina regardless of the spatial location of the stimulus. The saccadic deficits in this case were predominantly hemifield deficits, as was shown by the task in which 5° saccades in ipsilesional and contralesional directions were made from different orbital positions.

Varying the initial orbital position dissociates the retinal and spatial coordinates of the target, but preserves the equivalence between the target's retinal vector and the required eye movement vector. In the double-step task, the goal of the second saccade cannot be defined in retinotopic coordinates, because the first saccade modifies the relationship between the centre of gaze and the location of the target. In order to maintain the spatial accuracy of the second saccade, the extent of eye displacement associated with the first saccade has to be compensated for using information of extra-retinal origin.

The patient showed a unilateral impairment in this task but not in the direction that would be expected from a hemispatial deficit. When two stimuli were presented in sequence, one on each side of the central fixation point, the patient was able to generate a properly oriented leftward saccade following a prior rightward saccade. The leftward saccade undershot the target, as was expected from the mild retinotopic deficit. However, when the same locations were stimulated in the reverse sequence, the patient failed to make a rightward saccade following a prior leftward saccade. This impairment was neither spatial nor retinotopic. It was an impairment in compensating for an eye movement made in the contralesional direction: it seemed that the computation of a saccade in the 'normal' direction in response to a stimulus in the 'normal' visual field was aborted because of an inability to register the amplitude and direction of the immediately preceding saccade.

Can this pattern of results be accounted for without invoking extra-retinal factors? A perceptual rivalry effect is unlikely. It could explain that on two occasions the left-right target sequence triggered a right-left eye movement sequence, the ipsilesional target being responded to before the contralesional one. But on most trials the patient failed to respond to the ipsilesional target. An extinction effect, which was observed with simultaneous bilateral stimuli in patients with unilateral lesions (Bender and Teuber, 1947), would predict a pattern opposite to the one observed: the ipsilesional stimulus obliterating the contralesional one. Another possibility is that the trace of the right visual field target in 'working memory' was lost during the increased processing time of the first saccade to the left visual target. This is also unlikely since one would predict a more stable representation of ipsilesional than contralesional stimuli.

The results support the hypothesis that cortical sites in the frontal and parietal lobes are critical for performing spatial computations involving both retinal information and information corollary to eye movements. Area 8 neurons and neurons in the lateral intraparietal area, studied while monkeys performed a double-jump task, were found to encode a specific direction and distance relative to the centre of gaze, irrespective of the retinal location of the stimulus (Goldberg and Bruce, 1990; Goldberg *et al.*, 1990; Barash *et al.*, 1991). We recently demonstrated that, in the case of parietal cortex, this occurs because neural activity triggered by a previous visual input is remapped in conjunction with every eye movement into the coordinates of the current gaze location (Duhamel *et al.*, 1992). The present results indicate that such a mechanism is critical for double-step saccade performance, and perhaps more generally whenever spatial coding is required to transcend the inherent limitations of the retinal image.

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ACUTE OPTIC NEURITIS

A COGNITIVE AND MAGNETIC RESONANCE IMAGING STUDY

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SUMMARY

Forty-two patients with acute optic neuritis (ON) (mean duration of symptoms 14.5 d) were compared with a matched, normal control group on a battery of tests of attention and information processing speed. Approximately half the sample (55%) had brain abnormalities shown by magnetic resonance imaging (MRI) and were more impaired across a variety of tests compared with those patients without brain lesions or normal controls. There was no difference in psychometric performance other than the pegboard task between the normal control group and those ON patients without brain involvement. Significant correlations were found between total lesion area in the brain and some tests of attention. Results from the Symbol Digit-Substitution Test were particularly sensitive in this regard and could correctly identify 70% of the sample with brain lesions.

INTRODUCTION

The prevalence of cognitive impairment in patients with multiple sclerosis (MS) using standard psychometric tests has varied considerably, ranging from over 50% in a tertiary neurological setting (Peyser *et al.*, 1990) to less than 20% in those with mild physical disability (van den Burg *et al.*, 1987). The severity of cognitive impairment appears to be independent of the duration of the disease (Ivnik, 1978; Marsh, 1980) and degree of physical disability (Ron *et al.*, 1991). Although present in patients with relapsing-remitting MS (Beatty *et al.*, 1989), impairment may be more severe in those with a chronic-progressive disease course (Heaton *et al.*, 1985). These deficits are widespread, involving attention, memory and abstracting abilities with relative sparing of language functions (Rao, 1986) and contribute significantly to the overall disability experienced by patients (Rao *et al.*, 1991).

Recent studies of patients with clinically isolated lesions of the type seen in MS, frequently the harbinger of MS (Francis *et al.*, 1987; Miller *et al.*, 1989), have suggested that milder cognitive deficits may already be present in those whom clinical manifestations can be attributed to lesions in a single site (optic nerve, brainstem, spinal cord) outside the cerebral hemispheres (Lyon-Caen *et al.*, 1986; Callanan *et al.*, 1989). Widespread cerebral pathology is detected in about two-thirds of these patients (Ormerod *et al.*, 1987) and the observed cognitive deficits are likely to be the only manifestation of otherwise silent lesions.

The larger of these studies (Callanan *et al.*, 1989) carried out at the National Hospital

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for Neurology and Neurosurgery surveyed a heterogenous group of patients with optic neuritis (ON), brainstem and cord syndromes in whom pathology other than MS had been excluded. A decline from the expected premorbid intelligence quotient (IQ) and attentional deficits were detected when the subjects were compared with a disabled control group without evidence of brain damage. Many of these patients had been examined well after the onset of the clinically isolated syndromes and it is possible that further cerebral insults may have occurred in the absence of overt clinical manifestations and that cognitive impairment may have been absent if tested earlier. The present study is an attempt to answer this question by examining a group of patients with acute ON. Such a homogeneous sample has the added advantage of narrowing the range of perceptual and motor deficits which could have influenced the results of previous studies.

The weak association reported between degree of brain involvement on magnetic resonance imaging (MRI) and indices of cognitive dysfunction in patients with clinically isolated syndromes (Callanan *et al.*, 1989) may reflect the use of rating scales as opposed to direct quantification in documenting total lesion area (Rao *et al.*, 1989*a*). Therefore, a further aim was to investigate the correlations between severity of cognitive deficits and extent of MRI abnormalities taking advantage of quantification methods not previously available and, in addition, use magnetization parameters as an index of abnormality in normal-appearing white matter. Attentional deficits constitute the focus of this study as our previous results suggested that other cognitive deficits such as memory, while characteristic of patients with definite MS, are not impaired in those with ON.

METHODS

Subjects with a first episode of acute, unilateral ON of less than 5 wks duration were selected for the study. Those with vision of less than 6/6 in the unaffected eye were excluded, as were those with a history of alcohol/drug abuse or head injury leading to loss of consciousness or systemic disease. The sample comprised consecutive referrals to Moorfield's Eye Hospital where all subjects were screened by a neurologist to ensure inclusion criteria were met. In addition to recording demographic details, note was also made of any loss of colour vision and orbital pain. All subjects had a normal neurological examination except for signs of ON.

A control group of 36 healthy subjects, drawn from friends and relatives of the ON patients and staff from the Institute of Neurology, were used as a comparison. They were matched as a group to the ON patients with regards age, sex, premorbid IQ [using the National Adult Reading Test (NART)] and number of years of schooling. Patients and controls underwent a battery of psychometric tests presented in the visual and auditory mode, designed largely to detect deficits in attention and speed of information processing. All subjects and controls were tested in the morning to ensure uniformity of test conditions.

Psychometric assessment

The National Adult Reading Test (Nelson, 1982). This reading test has been shown to be resistant to the effects of cognitive decline and is considered a sensitive index of premorbid IQ.

Advanced Raven's Progressive Matrices (1) (Raven, 1958). This test was used to assess reasoning in the visuospatial modality. Raw scores were converted to an age-adjusted scaled score with a mean of 10.

The Purdue Pegboard Test (Purdue Research Foundation, 1948) This is a test of manual dexterity. Subjects were instructed to place the pegs in holes with each hand and then both hands simultaneously for periods of 30 s. The total number of pegs correctly placed over 90 s was taken as the score.

The Stroop Colour-Word Test (Stroop, 1935). A computerized version of this test was used to measure the ability to focus attention on one attribute of a compound stimulus (the colour in which words are written) and to ignore another competing attribute (the meaning of the word). A control condition was established prior to the Stroop test itself, measuring the speed and accuracy of identifying colours. Subjects were thus asked to name the colours of squares shown on the screen and speed of response was recorded. In the test condition, the names of colours written in different colours were presented. The subject was then asked to say the colour the word was written in and not the colour named by the word. The time to complete this task and the number of errors made were again recorded.

The Symbol-Digit Modalities Test (SDMT) (Smith, 1968). A computerized version of this test was used whereby nine different symbols each associated with a number were presented visually to the subject. Nine symbols at a time were shown to the subject in various orders and the subject had to respond by naming the number that corresponded to each symbol according to the original code. This approach minimizes a sensorimotor component to the procedure. Eight consecutive trials were administered at a constant time interval and presentation times for symbols and trials were the same for patients and controls. A total time for all eight trials and a mean time per individual trial were obtained. In addition, the total number of errors was also recorded.

The Paced Auditory Serial Addition Task (PASAT) (Gronwall, 1977). The task requires subjects to perform serial additions and to shift attention from old and no longer relevant items to new items. In the version used here, subjects were required to add 31 pairs of randomized digits presented in an auditory fashion so that each was added to the digit immediately preceding it. Two levels of difficulty were employed, with items being presented at 4 s and 2 s intervals. The number of errors for both trials were recorded.

The Paced Visual Serial Addition Task (PVSAT). As above, but items were presented visually on the computer monitor.

Speed of Letter Counting (Willison *et al.*, 1980). The time taken to count the number of As interspersed with other letters was used as a measure of visual attention.

Auditory Attention Test (Callanan *et al.*, 1989). From an auditory presentation, subjects were required to identify in correct order the alphabet which was embedded in a random collection of letters. The total number of false positives and omissions were taken to represent a measure of auditory attention.

Simple reaction time (SRT). This gave an index of basic psychomotor speed. The test comprised 60 trials for each hand. The imperative stimulus to which the subject had to react was the filling of a square either to the left (for the left hand) or the right (for the right hand) of a central blank square on the computer monitor. The subject reacted by pushing either the left or right button on a button box. The right-hand responses were completed before proceeding to the left-hand ones. Prior to the imperative stimulus, an arrow appeared in the central square pointing in the direction of the square to be filled. The arrow appeared 1.6 s, 0.8 s or 0.2 s before the imperative stimulus, respectively, each for 25% of the time. For the remaining 25% the arrow appeared simultaneously with the imperative stimulus. The order of the interval was randomly assigned to prevent the subject anticipating the exact occurrence of the stimulus. The interval between the end of one trial and the appearance of the arrow for the next trial was also randomly assigned between 1 s and 4 s.

Choice reaction time (CRT). The test comprised 80 trials. As in the SRT, the imperative stimulus to which the subject had to react was a filling of a square either to the left or right of the central blank square. A mixture of warned and cued CRT trials was used. In the warned trials, a cross appeared in the central square prior to the imperative stimulus. This indicated that the stimulus was about to appear but not which side. In the cued trials, the arrow appeared in the central square pointing in the direction of the square to be filled. The 80 trials were equally and randomly divided between warned and cued responses. Within each 40, half the responses were right and half left. The timing for the cross or arrow to appear prior to the imperative stimulus was the same as for the SRT and also randomly assigned to prevent anticipation.

In addition to the above psychometric battery, emotional state was assessed using the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983). This self-report scale has a subscale for both anxiety and depression (range of 0–21 for each) and attempts to avoid the influence of somatic complaints in rating the severity of emotional distress. Scores greater than or equal to 10 on either the anxiety or depression subscale were indicative of psychiatric 'caseness'.

The Social Stress and Support Interview (Jenkins *et al.*, 1981) was used to determine the amount of stress or support as perceived by the subject. Scores of +1 for support, 0 if neither support nor stress were evident and −1 for stress were assigned to the following areas: work, finances, housing, social contacts, marriage and family relationships.

All subjects were tested and scanned on the same morning. The psychological battery took approximately 1 h to administer.

Magnetic resonance imaging assessment

Subjects underwent multislice MRI of the brain with a 0.5 Tesla Picker superconducting system. Contiguous, axial (transverse) slices with a 5 mm thickness were obtained using a spin echo ($SE/_{1500/60}$) sequence.

A procedure to detect the total lesion area was derived from in-house software. All lesions were identified and marked on the hard copy. The images from the magnetic tape were then viewed in the Picker SUN workstations (SUN Microsystems Inc., Mountain View, CA, USA) and each of the 24 individual brain slices enlarged to full screen size. Using the hard copy to confirm the presence and site of lesions, the interface window was adjusted to improve contrast between lesion and surrounding brain tissue. A trace was then manually drawn around individual lesions and their anatomical location recorded The area within the trace corresponded to the area in pixels occupied by that particular lesion. Having analysed all 24 slices in this manner, the individual lesion areas were summed to give a total lesion area. A total periventricular lesion area was also calculated. Intra-rater reliability (test-retest) revealed a variance of approximately 3% for patients with a high lesion load (in excess of 20 lesions) and 6% for those with a more moderate load.

T_1 and T_2 relaxation times were calculated from algorithms supplied by the manufacturer. As the first 12 consecutive patients were part of another research protocol, limitations on scanning time meant that relaxation times were obtainable for only the remaining 30 of the 42 ON subjects. A single slice of normal-appearing frontal white matter was chosen for this purpose using two spin echo ($SE/_{1500/40}$, $SE/_{1500/120}$) and an inversion recovery ($IR/_{150/40/500}$) sequence. Analysis was undertaken using the automated program 'ANALYZE' (Mayo Foundation Biodynamic's Research Unit, 1986). A manual trace was used to outline the area of frontal white matter, delineating it from cortical grey matter and cerebrospinal fluid. The interface window on the T_1-weighted images was adjusted to give maximum tissue contrast for this purpose. The anatomical trace thus obtained was superimposed on the T_2-weighted image, which had greater sensitivity in demonstrating the presence of MS plaques, and the interface window again adjusted to maximize the contrast between lesion and normal-appearing white matter. With the additional help of the printed MRI pictures, the outlines of the lesions (if present) were traced manually. The aim of this procedure was to define the largest possible area of normal-appearing frontal white matter demarcated from cortex, cerebrospinal fluid and lesions, from which T_1 and T_2 relaxation times could be obtained.

A second, separate control group of healthy volunteers ($n = 30$) matched for age and sex were scanned over the same period as the patient group to provide normative data for the relaxation times. The validity of these measurements was checked using phantoms which controlled for machine drift over time.

Statistical analysis

Both parametric and non-parametric analyses were used, depending on the distribution of the particular variables. Thus, for demographic comparisons two sample t tests or χ^2 tests were utilized, the median and range being quoted for all non-parametric analyses. Two-tailed P values are reported throughout.

Comparisons between three groups (i.e. control and ON subjects with and without brain lesions) were undertaken using either one-way analysis of variance (ANOVA) or Kruskal-Wallis ANOVA, depending on variable distributions. To reduce the experimentwise error, only those variables significant at the 5% level were further analysed with the Tukey-Kramer multiple comparisons method to ascertain where specific group differences lay. The Tukey-Kramer method was preferred as it is the method of choice for dealing with unequal sample sizes and is more powerful than methods such as the Bonferroni for pairwise comparisons. For *post hoc* analysis of statistically significant Kruskal-Wallis tests, Mann-Whitney comparisons were done.

Correlations between variables were assessed with either the Pearson's or Spearman's Rank correlation coefficient.

RESULTS

Forty-two consecutive patients met the selection criteria and were matched to 36 controls with respect to age, sex, number of years of education and premorbid IQ

(Table 1). Seven of the patients and four of the controls were left handed. The mean duration of symptoms was 14.5 d (range 3–35 d). Thirty-three patients had experienced loss of all or part of their visual field in the affected eye, while 30 had experienced orbital pain. Twenty-four patients reported their symptoms were improving at time of testing, 11 thought symptoms had remained constant since presentation, while seven noted deterioration. Aggravating factors such as exercise were reported by 14 subjects. It should be emphasized that apart from symptoms of ON, the neurological examination was entirely normal for the entire sample.

TABLE 1 DESCRIPTIVE CHARACTERISTICS OF THE PATIENT AND CONTROL SAMPLE

	ON subjects (n = 42) Mean (SD)	*Control subjects (n = 36) Mean (SD)*	*t test/χ^2*	*Significance*	*95% confidence intervals*
Sex M:F	20:22	19:17	$\chi^2 = 0.05$	NS	
Age (yrs)	29.8 (6.8)	31.3 (11.1)	$t = -0.69$	NS	−5.6 to 2.61
Years of schooling	12.0 (1.5)	12.3 (1.6)	$t = -0.74$	NS	−0.98 to 0.45
Premorbid IQ (NART)	112.6 (8.6)	115.6 (6.8)	$t = -1.7$	NS	−6.7 to 0.54

SD = standard deviation; NS = not significant.

Magnetic resonance imaging results

Twenty-three subjects (55%) had high signal abnormalities on MRI. The median total lesion area was 23 pixels (0.32 cm^2) [range = 0–1387 pixels (19 cm^2); mean = 128.6 pixels (1.76 cm^2); SD = 261.52 pixels (3.58 cm^2), respectively]. There were no significant differences in either T_1 or T_2 times between the ON group and 30 matched control subjects [T_1 patients and controls: 419 ms (12.9) vs 421.1 ms (11.7); T_2: 76.7 ms (2.3) vs 76.6 ms (3.3)].

Comparing relaxation times in those subjects with (n = 19) and without (n = 11) high signal intensity lesions on MRI revealed the former to have higher T_1 values (mean 421.7 vs 416.9) but this did not reach statistical significance. Total lesion area did not correlate significantly with either T_1 or T_2 relaxation times.

Comparisons in psychometric performance between control subjects and ON subjects with and without brain lesions on MRI

Comparisons using ANOVA were undertaken between control subjects (n = 36) and those subjects with (n = 23) and without (n = 19) MRI abnormalities. The three groups were matched with respect to demographic details and premorbid IQ. There were no differences in the number of patients from the two ON groups who were experiencing orbital pain or visual acuity problems at the time of testing.

A number of differences emerged between the three groups, patients with ON and a normal MRI generally occupying an intermediate position between those of the control subjects and ON patients with observable brain lesions (Table 2).

The Purdue Pegboard Test. No differences were present between the two ON groups who both peformed significantly more poorly than the normal control group [F(2,75) = 9; $P < 0.0001$]. *Post hoc* analysis confirmed a significant ($P < 0.05$) difference between the control and both ON groups.

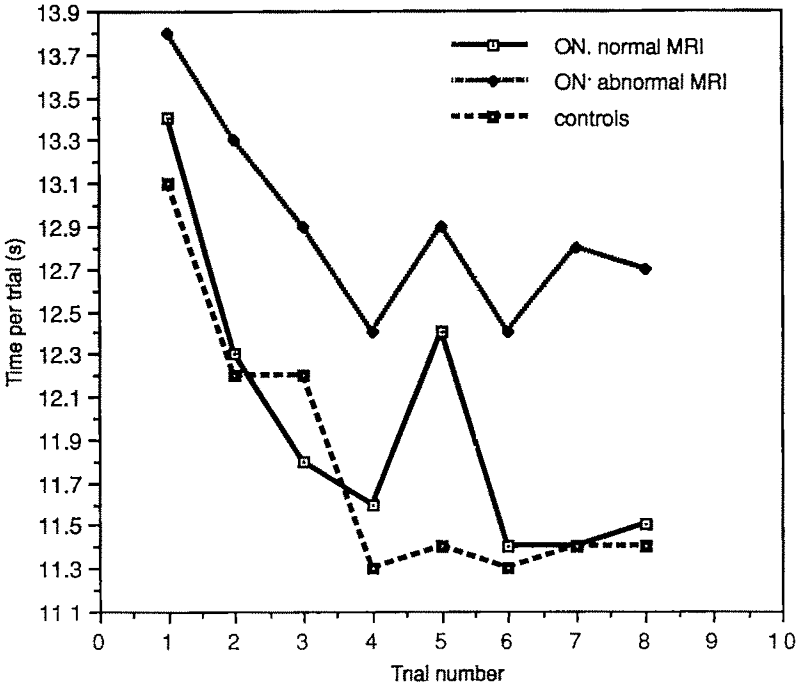

FIG 1 Results from the Symbol-Digit Modality Test for ON patients and control subjects.

The Stroop Colour-Word Test. A 0.5 s difference between the ON group with and without brain lesions in the control condition (speed of colour recognition) had increased to 3 s for the full Stroop paradigm, but did not prove statistically significant due to a larger standard deviation in the brain lesion group. Re-analysis using non-parametric statistics gave a similar result. There was no significant group×condition interaction [F(4,150) = 1.48; $P < 0.2$: ANOVA].

The Symbol-Digit Modalities Test. The patients with observable brain lesions were slower than the other two groups on total time taken to complete the eight trials. A significant time effect, independent of group was apparent across the eight trials [F(7,525) = 16.1; $P < 0.0001$: ANOVA]. There was, however, no significant group×time interaction [F(14,525) = 1.47; $P < 0.12$: ANOVA], implying that changes in speed across the eight trials were consistent for all three subject groups (Fig. 1). *Post hoc* analysis failed to demonstrate significant differences between any two groups.

The Paced Auditory Serial Addition Task. Combining results from the 4 s and 2 s stimuli trials, significant differences were apparent across the three groups [F(2,73) = 5.9; $P < 0.004$: ANOVA]. There was no significant group×time interaction [F(2,75) = 1.08; $P < 0.34$: ANOVA]. *Post hoc* analysis revealed that at the 4 s stimulus, significant differences were present between the ON group with brain lesions and both the control subjects and those with ON and a normal MRI. At the 2 s stimulus test, however, a significant difference was only apparent between the healthy control subjects and those with ON and brain lesions.

TABLE 2 COMPARISONS IN COGNITION, PSYCHIATRIC STATUS AND SOCIAL STRESS BETWEEN CONTROL AND ON SUBJECTS WITH AND WITHOUT BRAIN LESIONS ON MRI

	Group 1 controls (n = 36)	*Group 2 ON with normal MRI (n = 19)*	*Group 3 ON with abnormal MRI (n = 23)*	*One-way ANOVA/ Kruskal-Wallis*	*Significance*	*1 vs 2*	*1 vs 3*	*2 vs 3*
		Mean (SD) or median (range)						
Pegboard test	41.8 (4.4)	37.3 (4.6)	37.7 (4.6)	F = 9.0	*P* < 0.0001	+	+	•
Raven's Matrices	11.4 (3.0)	10.5 (2.5)	10.1 (2.6)	F = 1.9	NS	•	•	•
Stroop (C) test	12.3 (2.3)	12.3 (2.3)	12.8 (2.6)	F = 0.27	NS	•	•	•
Stroop test	22.4 (4.8)	22.1 (4.9)	25.1 (7.0)	F = 2.1	NS	•	•	•
SDMT (mean)	11.8 (1.8)	12.0 (1.0)	12.9 (1.9)	F = 3.0	*P* < 0.06	•	•	•
Letter counting speed	14.1 (3.8)	14.2 (2.4)	15.0 (2.8)	F = 0.59	NS	•	•	•
PASAT (4 s)	2.0 (0–8.0)	1.0 (0–7.0)	3.0 (0–14.0)	$\chi^2 = 7.3$	*P* < 0.03	•	+	+
PASAT (2 s)	7.9 (3.7)	8.1 (4.4)	11.2 (5.4)	F = 4.3	*P* < 0.01	•	+	•
PVSAT (4 s)	0.5 (0–6.0)	0 (0–5.0)	1.0 (0–15.0)	$\chi^2 = 0.14$	NS	•	•	•
PVSAT (2 s)	4.8 (3.4)	5.9 (4.6)	7.8 (4.6)	F = 3.7	*P* < 0.03	•	+	•
Auditory attention	1.0 (0–5.0)	1.0 (0–5.0)	1.0 (0–7.0)	$\chi^2 = 2.2$	NS	•	•	•
HAD anxiety	5.9 (3.9)	6.6 (2.2)	5.1 (3.4)	F = 0.9	NS	•	•	•
HAD depression	2.0 (0–10.0)	3.0 (0–9.0)	2.0 (0–9.0)	$\chi^2 = 1.5$	NS	•	•	•
SSSI	3.9 (1.6)	4.1 (1.6)	4.0 (1.9)	F = 0.06	NS	•	•	•

SDMT = Symbol-Digit Substitution Test, PVSAT = Paced Visual Serial Addition Task, PASAT = Paced Auditory Serial Addition Task, HAD = Hospital Anxiety and Depression Scale, SSSI = Social Stress and Support Interview. Time scores for the Stroop, SDMT and Letter Counting are in seconds, scores for the PVSAT, PASAT and Auditory Attention tests are number of errors made, NS = not significant, 1 vs 2 = *post hoc* comparisons between controls and ON group with normal MRI, 1 vs 3 = *post hoc* comparisons between controls and ON group with abnormal MRI, 2 vs 3 = *post hoc* comparisons between ON groups with normal and abnormal MRI. + significant differences ($P < 0.05$) between two groups (*post hoc* Tukey-Kramer analysis), •Not statistically significant

The Paced Visual Serial Addition Task. Differences across the three groups were present at the 2 s, but not 4 s stimulus. *Post hoc* analysis demonstrated that this difference lay between the ON group with brain lesions and the healthy control subjects. Combining results from both time trials, no group differences were found [F(2,75) = 2.8; $P < 0.07$: ANOVA]. The group×time interaction was, however, significant [F(2,75) = 3.29; $P < 0.04$: ANOVA], with more errors being made on the 2 s trial particularly by those patients with an abnormal MRI.

In general, both patient and control subjects considered the auditory tasks to be the more difficult irrespective of whether the stimulus was 4 s or 2 s and this reflected in the increased numbers of errors on the PASAT as opposed to the PVSAT.

Reaction time tests. The scores for the SRT and CRT are shown in Table 3.

There were no group differences for the SRT or CRT (warned or cued) tests. There was a significant group×time (warning signal interval) interaction for the SRT [F(6,222) = 2.66; $P < 0.02$: ANOVA], but not the CRT tests. This was due to the ON group without brain lesions reacting slower than the other two groups to stimuli presented without warning. This group then proceeded to get progressively quicker as the warning interval increased while the other two groups reached a plateau after 0.8 s.

A multivariate analysis was performed investigating the interaction between group (control or ON patients with or without lesions), modality (SRT or CRT; warned and cued), side of response (right or left) and time (0, 0.2, 0.8, 1.6 s). The group× modality×side×time interaction was not significant [F(12,444) = 0.95; $P < 0.5$:

TABLE 3 REACTION TIME TEST RESULTS FOR ON PATIENTS WITH AND WITHOUT AN ABNORMAL MRI AND CONTROL SUBJECTS

	Controls (n = 36) Mean (SD)	*ON with normal MRI (n = 19) Mean (SD)*	*ON with abnormal MRI (n = 23) Mean (SD)*
SRT (0 s)	0.35 (0.05)	0.37 (0.06)	0.35 (0.1)
SRT (0.2 s)	0.26 (0.04)	0.28 (0.05)	0.28 (0.09)
SRT (0.8 s)	0.24 (0.04)	0.25 (0.05)	0.27 (0.09)
SRT (1.6 s)	0.24 (0.05)	0.24 (0.04)	0.25 (0.09)
WCRT (0 s)	0.44 (0.05)	0.46 (0.07)	0.46 (0.09)
WCRT (0.2 s)	0.35 (0.05)	0.36 (0.05)	0.38 (0.08)
WCRT (0.8 s)	0.32 (0.06)	0.34 (0.06)	0.32 (0.05)
WCRT (1.6 s)	0.32 (0.06)	0.32 (0.05)	0.33 (0.06)
CCRT (0 s)	0.43 (0.05)	0.43 (0.06)	0.44 (0.07)
CCRT (0.2 s)	0.31 (0.05)	0.32 (0.06)	0.32 (0.08)
CCRT (0.8 s)	0.28 (0.06)	0.30 (0.10)	0.28 (0.07)
CCRT (1.6 s)	0.26 (0.05)	0.26 (0.05)	0.27 (0.06)

SRT = simple reaction time; WCTR = warned choice reaction time, CCRT = cued choice reaction time.

ANOVA]. The only significant interactions were modality×time [F(6,444) = 12.7; $P < 0.0001$: ANOVA], side×time [F(3,222) = 3.8; $P < 0.01$: ANOVA] and modality×time×side [F(6,444) = 2.4; $P < 0.03$: ANOVA], indicating that all subjects irrespective of control or ON status were quicker on SRT tasks as opposed to CRT and that right-hand responses (dominant side in the majority of cases) were quicker than left.

No group differences were present for the remaining psychometric tests, namely the Raven's Matrices, Visual Attention (letter-counting speed) and Auditory Attention Task (alphabet discrimination).

Emotional state

Eight subjects had a premorbid history of psychiatric complaints, five of whom had been treated at an out-patient clinic. These disorders comprised adjustment disorders and minor affective disorders. None of the controls had a past psychiatric history.

There were no differences in scores on the Hospital Anxiety and Depression Scale between the ON subjects and the matched control group, nor were any differences apparent when those subjects with an abnormal MRI were compared with either those without or the control group (Table 2). Five subjects with ON met the criteria for psychiatric 'caseness' as opposed to seven control subjects. The five ON patients were classed as psychiatric 'cases' by virtue of their scores on the anxiety subscale exceeding the threshold and none were significantly depressed. A similar situation existed for the control group with six of the seven psychiatric 'cases' exceeding the cut-off point for anxiety only.

Optic neuritis subjects, with or without brain involvement on MRI were no more likely to perceive their lives as being more stressful or their social support less adequate than the control group (Table 2).

Relationship between cognition and MRI abnormalities

Positive correlations (Spearman's Rank) between total lesion area and mean/total time for the SDMT ($r = 0.46$; $P < 0.01$) and 4 s PASAT ($r = 0.48$; $P < 0.001$) were found indicating that those with more extensive brain involvement performed worse. Relaxation times did not correlate with any indices of cognition or psychiatric status.

Sensitivity of the cognitive tests in detecting brain damage

Starting with the premise that those ON subjects who had deficits on psychometric testing were more likely to have brain involvement, the various tests were re-examined to investigate which were the most sensitive and specific predictors of cerebral involvement. A discriminant function analysis was used for this purpose. The following variables were selected on the basis of results from the ANOVA across control and patient groups (*see* Table 3): the Stroop test, SDMT (total time), PVSAT (4 s and 2 s stimuli), PASAT (4 s and 2 s stimuli) and Raven's Matrices, the scores dichotomized about their mean or median depending on their distribution and entered in the analysis. A combination of three variables were found to predict with a 76% accuracy whether subjects would have brain lesions on MRI or not. These were the SDMT (total time), PASAT (4 s stimuli) and PVSAT (4 s stimuli). Of the three, the SDMT was the most powerful predictor, correctly grouping almost 70% of cases.

DISCUSSION

Comparisons between ON patients with and without brain lesions and healthy control subjects revealed a number of differences. In terms of raw scores, patients with ON and a normal MRI occupied a position intermediate between healthy control subjects and ON patients with an abnormal MRI. This, however, only reached statistical significance for three tests, namely the PVSAT (2 s), PASAT (2 s) and PASAT (4 s) and only the latter could distinguish between ON patients with and without an abnormal MRI. As subjects with brain lesions are most at risk for the early development of MS (Miller *et al.*, 1988), our results based on more stringent selection criteria and improved imaging techniques, replicate those of Callanan *et al.* (1989) and reveal deficits in attention to be one of the earliest features of demyelinating disease.

There was no MRI evidence (either visible lesions or abnormal relaxation times) to suggest brain abnormalities in approximately half the ON sample. Differences between this group and control subjects on the pegboard test could not be attributed to impaired motor speed given the former's slightly superior performance of the SRT test and this left impaired visual acuity in the ON group as the likely explanation. The absence of brain abnormalities in the ON subgroup was further reflected by their similar performance to the control group on all remaining psychometric tests, where no statistically significant differences were present.

There were no differences between the two ON groups regarding visual acuity and this is supported by their almost identical performances on the pegboard task. There was, however, evidence to suggest that the patients with an abnormal MRI had additional deficits directly related to the presence of their brain lesions. in comparison to the ON group with a normal brain, they made significantly more errors on a relatively slow test of auditory attention (4 s PASAT), while results from a group×time interaction revealed their greater difficulty moving from a 4 s to a 2 s visual serial addition task.

The fact that in our sample psychometric differences between groups were present on some (serial addition tests), but not other tests (letter counting, alphabet task) within the same sensory modality could be due to the greater sensitivity and complexity of the former. Thus, failure by the ON group with brain lesions to perform adequately on the serial addition tasks may also reflect abnormalities in speed or efficiency of information processing, a function noted to be slowed in patients with definite MS (Rao *et al.*, 1989*b*) and considered anatomically distinct from that of attention (Posner and Petersen, 1990). Tasks like the PASAT which tap a number of different cognitive processes including retrieval from short-term memory, make it a sensitive discriminator of cognitive speed between brain-damaged patients and control, particularly when stimuli are presented more quickly (Litvan *et al.*, 1988). We noted a similar effect in our study where a group×time interaction was present for the PVSAT. Tests that were not time dependent, namely the Raven's Matrices, failed to distinguish between the groups and therefore lend indirect support to the above explanation. In interpreting our results, however, some caution is needed. While *post hoc* Tukey-Kramer analyses controlled for multiple comparisons, the possibility remained that at the 5% level of significance, one of our positive findings may have been due to chance alone.

We did not find any group differences between the ON and control subjects on reaction time tests other than a group×time effect of the SRT tasks which cannot be readily explained given the pattern of results from the other tests. In definite MS, abnormalities in reaction times are most marked in those patients with a chronic-progressive course (Elsass and Zeeberg, 1983), longer disease duration and greater physical disability (Jennekens-Schinkel *et al.*, 1988*a*). It is therefore not surprising that in a sample of patients with acute ON, representing early demyelinating disease, deficits in reaction times were not apparent. Increasing task complexity (i.e. changing from a simple to choice paradigm) did not lead to a differential increase in reaction times in the ON group, something also noted by Jennekens-Schinkel *et al.* (1988*b*) in subjects with definite MS. In addition, our ON cohort had the ability to overcome the effects of fatigue induced by the 80 trials of the CRT task.

Fifty-five percent of our ON patients had brain lesions at presentation, a figure in agreement with previous reports (Miller *et al.*, 1988), almost exclusively confined to hemispheric white matter. Attention is subserved by large-scale neurocognitive networks dependent on fibre bundles linking various cortical and subcortical structures (Mesulam, 1990) and it follows that lesions scattered widely throughout the white matter can cause considerable disruption to the functioning of the systems. This is reinforced in our study by the association between extent of the lesion area and degree of psychometric deficits.

The robust correlation between cognitive deficits and total lesion area on MRI has not been previously reported in patients with clinically isolated lesions, the reasons being twofold. First, more sensitive tests of attention were employed than previously (Callanan *et al.*, 1989), the SDMT being particularly noteworthy in this regard (Beatty and Goodkin, 1990) and secondly, improved methods of MRI analysis were used with quantification of total lesion area proving superior to a rating scale approach (Rao *et al.*, 1989*a*). This positive correlation refutes the myth of the 'silent' MS lesion and demonstrates cognitive dysfunction to be a more sensitive marker of brain involvement than neurological signs and symptoms (Jacobs *et al.*, 1986; Thompson *et al.*, 1990). The ability of three psychometric tests to accurately discern the presence of brain lesions in over three-quarters of the ON sample, while of obvious limited value in individual cases, nevertheless reinforces the positive association between brain involvement and psychometric dysfunction.

Irrespective of the presence of brain abnormalities, the ON group was characterized by a low psychiatric morbidity no different from that of their control group and equal to that reported in general population studies (Andrews *et al.*, 1977). This agrees with our previous studies that found a low psychiatric morbidity in a mixed group of patients with clinically isolated syndromes when first seen (Logsdail *et al.*, 1988) and at follow-up 5 yrs later when no significant neurological deterioration had occurred (Feinstein *et al.*, 1992). If, however, clinically definite MS develops, more marked psychopathology is associated with a chronic-progressive course and its attendant increased physical disability and perceived social stress.

While there is evidence from studies of patients with definite MS that cognitive dysfunction affects a wide variety of occupational, social, sexual and basic activities of daily living (Rao *et al.*, 1991), it seems unlikely that the same applies to our sample given the mild severity of their deficits. The majority of patients were still working and had not experienced social or occupational difficulties other than that related to impaired visual acuity. Nevertheless, there does appear to be sufficient evidence in patients with acute ON and demonstrable brain disease suggesting deficits in attention and/or information processing speed are present early in the demyelinating process, predating the development of further neurological signs and symptoms.

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THE MECHANISM OF FACIAL SWEATING AND CUTANEOUS VASCULAR RESPONSES TO PAINFUL STIMULATION OF THE EYE

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SUMMARY

The vascular response in the forehead and cheeks to irritating the eye with soapy water was measured in 15 normal subjects. Electrodermal activity, which reflects sweating, was also measured from both sides of the forehead. The mechanism of the response was studied in 15 patients with a unilateral lesion of the facial nerve blocking parasympathetic outflow.

Pulse amplitude usually increased briefly on both sides of the forehead after the soap was placed in the eye; the response persisted for several minutes on the ipsilateral side after the soap had been washed from the eye. A facial nerve lesion blocked the vascular response on the lesioned side to stimulation of either eye. No consistent change in pulse amplitude was recorded from the cheeks, although a response was observed in a few subjects. Electrodermal responses to ocular irritation were generally larger on the ipsilateral than contralateral side of the forehead; in patients with facial palsy, electrodermal responses were greater on the normally innervated side than on the lesioned side.

The findings suggest that irritating the eye induces a trigeminal-parasympathetic vasodilator reflex and local sweating. The restricted distribution of the response indicates that separate parasympathetic vasodilator reflexes might operate for each division of the trigeminal nerve.

INTRODUCTION

Irritating the eye causes local reddening, constriction of the pupil, and an increase in intra-ocular pressure (Mandahl and Bill, 1981). Vascular changes in surrounding skin have not been studied.

Pain may also induce local sweating. Bickford (1938) and Wilkins *et al.* (1938) reported that 1–2 min of painful electrical stimulation of the skin produced sweating in a radius of 3–8 cm around the electrodes. This response required intact postganglionic sympathetic fibres, and was elicited most easily in subjects who were on the verge of sweating, or when the skin was warm. Wilkins *et al.* (1938) stated that crushing the skin did not produce sweating detectable by the starch-iodine technique, but this method is insensitive to minor fluctuations in sweating.

The effect of painful ocular stimulation on blood flow and sweating in surrounding skin was studied in the present experiment. Skin conductance was recorded to detect subtle changes in facial sweating. The nature of the response was studied in normal subjects, and its mechanism was investigated in patients with a unilateral facial nerve lesion compromising parasympathetic outflow.

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METHOD

Subjects

The normal response to ocular irritation was measured in nine female and six male undergraduate university students aged between 17 yrs and 39 yrs (mean age 21 yrs). The mechanism of the response was investigated in seven males and eight females aged between 31 yrs and 64 yrs (mean age 49 yrs) with unilateral facial palsy produced during removal of an acoustic neuroma 4–11 mths previously (mean 40 mths). Shortly after the operation each patient had a lateral tarsorrhaphy to protect the cornea from drying. Nine of the 15 patients had noticed some return of lacrimation; in the two patients with the longest history of facial palsy (89 mths and 111 mths) the symptomatic eye now watered more than the opposite eye, particularly in response to gustatory stumuli or sunlight. Schirmer's test confirmed that lacrimation was greater on the symptomatic side in these two cases whereas the eye was dry in the other 13 patients.

Each subject provided informed consent for the procedures, which were approved by the university ethics committee.

Procedures

Subjects sat on a comfortable chair in an air-conditioned room maintained at 21 ± 1°C. The forehead and cheeks were cleaned with soap and warm water and dried thoroughly before recording devices were attached.

Pulse transducers (photoplethysmographs, Grass Instrument Company, Quincy, MA, USA) were attached with adhesive washers to each side of the forehead, 1 cm above the eyebrows and 4 cm from the midline, and to the cheeks, 3 cm below the eyes and 5 cm from the midline. Pulse amplitude was displayed on a four-channel Grass chart recorder.

Electrodermal activity was recorded from each side of the forehead by passing a 10 μA current between silver-silver chloride electrodes (internal diameter 8 mm), attached by adhesive washers 1 cm above the eyebrows near the midline, and 6 cm from the midline. Skin resistance was detected by two Grass 7P1 preamplifiers in the PGR mode. To eliminate electrical interaction between the two recording sites, at any one instant current was applied on only one side of the forehead. This was achieved by a device which switched between channels 25 times/s. Electrodermal activity was displayed on a two-channel Grass chart recorder.

After the subject had been sitting quietly for 15 min, one drop (approximately 0.07 ml) of soapy water was placed in the conjunctival sac of one eye. The soapy water was prepared by mixing 1 ml of liquid bathroom soap in 4 ml of 0.9% saline. In seven patients with a facial nerve lesion, the ipsilateral eye was tested first. Physiological activity was recorded for 1 min, and then the soap was washed out of the eye with 0.9% saline. The subject rated the intensity of pain on a scale ranging from 'not painful' (0) to 'worst pain imaginable' (10). The procedure was repeated for the other eye 5 min later.

Facial sweating and flushing to body heating were also investigated in patients with a facial nerve lesion. To induce thermoregulatory responses, warm air from a fan heater was blown under blankets wrapped around the patient. Heating continued for 13 to 44 min (mean 24 min) until facial sweating was visible.

Data reduction and statistical analysis

Pulse amplitude was measured for 30 s before and 60 s after soap was placed in the eye and 1 min and 5 min after washing the soap from the eye. Changes in pulse amplitude were expressed as a percentage of the amplitude recorded immediately before the first eye drop, because the pulse transducer detected only relative changes in cutaneous blood flow.

The skin resistance level before placing the drop of soapy water in the eye was used as a baseline. The immediate response to the eye drop was defined as the largest decrease in resistance during the next 30 s. The response during the following 30 s, and levels of skin resistance 1 and 5 min after the soap was washed from the eye, were also measured. Since skin conductance is directly related to sweating whereas skin resistance is inversely related (Lykken and Venables, 1971), values were transformed to conductance units (μs). Skin conductance responses were then calculated as the difference between levels at each data point and the baseline.

Separate analyses of variance (MANOVA programme, SPSSX) were computed for responses during stimulation, and return to baseline after the soap was washed from the eye. In normal subjects, comparisons were made between the two sides (stimulated versus contralateral), the time course of the response, and between the first and second eye drops. In patients with facial palsy, the response on the lesioned side was compared with the response on the normally innervated side. Saline usually spilled down the cheek when soap was rinsed from the eye. Since this probably influenced vascular activity cheek pulse amplitude data 1 and 5 min after rinsing the soap from the eye were not included in these statistical analyses.

RESULTS

Normal responses to ocular irritation

Pain ratings. Ratings ranged between two (mildly painful) and nine (extremely painful), with a mean rating of 5.4 (SD ± 1.5). Group and individual ratings were similar for the first and second eye drops.

Vascular response. Pulse amplitude increased on both sides of the forehead immediately after the soapy eye drop was administered (Fig. 1). This response persisted on the ipsilateral side of the forehead after the soap was washed from the eye, but not on the contralateral side (Fig. 1). The local vascular response was observed in 14 of 15 subjects; it may be relevant that the face of the unresponsive subject was inflamed by eczema.

In general, forehead pulse amplitude increased more on the side ipsilateral to stimulation than on the contralateral side, both during and after stimulation [F(1,14) = 5.76, $P < 0.05$ and F(1,14) = 9.94, $P < 0.01$, respectively]. The response was greater during the 30 s after the eye drop was instilled than during the following 30 s [F(1,14) = 21.66, $P < 0.001$], and gradually subsided from the first to the fifth minute after the soap was washed from the eye [F(1,14) = 7.95, $P < 0.05$]. The second drop

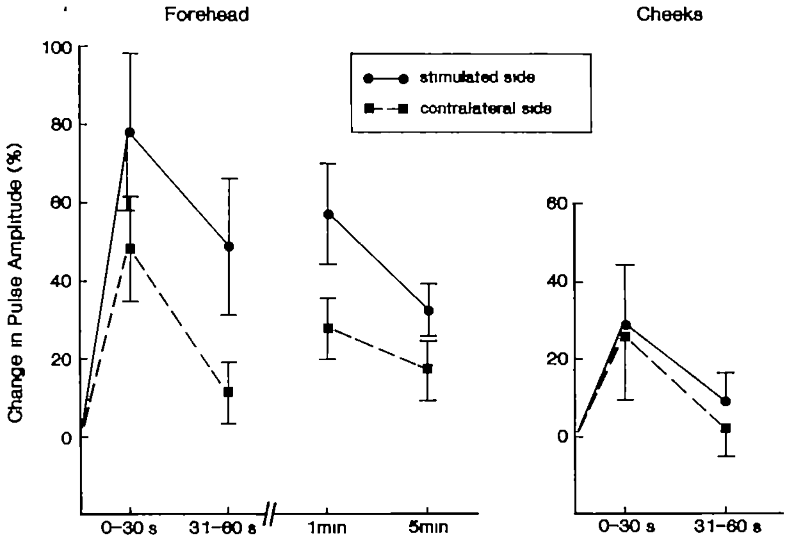

FIG. 1. Vascular responses in the facial skin to ocular irritation. The soapy eye drop induced a persistent response in the ipsilateral forehead circulation, and a transient response in the contralateral forehead and cheeks. Bars represent the standard error of responses.

of soapy water produced a response similar to the first; on the irritated side, pulse amplitude increased 61% to the first eye drop and 65% to the second.

In contrast to the forehead, vascular responses in the cheeks did not differ significantly between the stimulated and contralateral sides (Fig. 1). In fact, cheek pulse amplitude did not change consistently from baseline after the soapy eye drop was administered, although a response was observed in a few subjects.

Electrodermal response. Skin conductance generally increased slightly on both sides of the forehead after the soapy eye drop was placed in one eye, more so on the stimulated side (Fig. 2). In one unusually responsive subject skin conductance responses to the first eye drop were more than 25 times greater than the mean response in the other 14 subjects; the response was twice as great on the stimulated side. When data from this unusually responsive subject were excluded, the average increase in skin conductance during both eye drops was significantly greater on the stimulated side [$F(1,13) = 14.27$, $P < 0.01$]. The difference in response between the two sides of the forehead was marginally greater 31–60 s after the eye drop was instilled than during the first 30 s [$F(1,13) = 3.99$, $P < 0.1$]. The second eye drop induced a response similar to the first. After the soap was washed from the eye, skin conductance levels did not differ significantly from baseline on either side of the forehead.

Facial nerve lesion

Pain ratings. Most patients with facial palsy reported greater pain on the lesioned side [mean rating 7 ± 2.6 compared with 5.5 ± 1.5 on the normally innervated side, $t(14) = 2.89$, $P < 0.05$]. However, one patient reported less pain on the symptomatic side, and another rated the pain as mild on both sides.

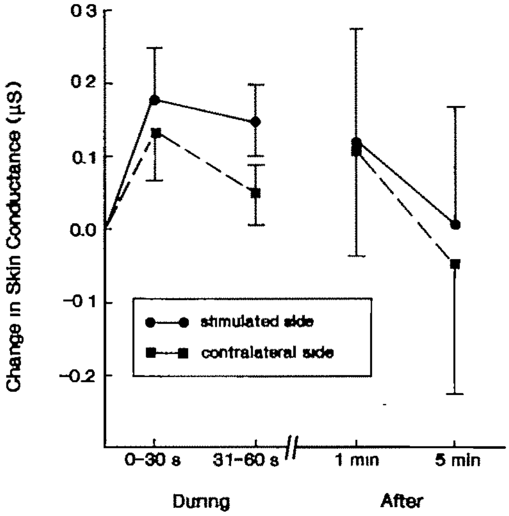

FIG. 2. Electrodermal response in the forehead to ocular irritation. Increases in skin conductance 31–60 s after the soapy eye drop was placed in the eye were slightly larger on the stimulated side than on the contralateral side. In one other patient excluded from analyses, skin conductance increased 8.63 μS and 0.31 μS on the stimulated side in trials 1 and 2, respectively, and 4.43 μS and 0.81 μS on the contralateral side. Bars represent the standard error of responses

Vascular and electrodermal responses to ocular irritation. The facial nerve lesion blocked vascular responses to ocular irritation (Fig. 3). Increases in pulse amplitude were greater on the normally innervated side of the forehead than on the lesioned side both during and after stimulation [F(1,14) = 17.06, $P < 0.001$ and F(1,13) = 20.18, $P < 0.001$, respectively]. The facial nerve lesion also prevented the response to contralateral ocular irritation (Fig. 3).

In the eight patients tested, the increase in cheek pulse amplitude was marginally greater on the normally innervated side during ocular irritation (Fig. 4) [F(1,7) = 3.65, $P < 0.1$].

Baseline levels of skin conductance did not differ significantly between the lesioned and normally innervated sides of the forehead in patients with facial palsy. In general, ipsi- and contralateral increases in skin conductance were greater on the normally innervated side of the forehead than on the lesioned side, both during and after ocular irritation. However, the immediate ipsilateral response to the eye drop was similar on the lesioned and normally innervated sides (Fig. 5). Thus, the difference was greater 31–60 s after soap was placed in the eye than during the first 30 s [time by side interaction F(1,14) = 9.61, $P < 0.01$]. The difference in response between the two sides persisted after the soap was washed from the eye [F(1,13) = 7.26, $P < 0.05$].

The patient with the longest history of facial palsy showed a different pattern of response to other patients; ocular irritation induced increases in pulse amplitude on both sides of the forehead, and greater increases in skin conductance on the symptomatic side.

Thermoregulatory responses. Vascular pulsations increased symmetrically in the forehead and cheeks during body heating (Table 1). Skin conductance recorded from the forehead also increased symmetrically (Table 1). On inspection of the face, sweating was observed on both sides of the forehead (14 patients), cheeks (nine patients), across the upper lip (10 patients) and on the chin (four patients). In one patient less sweat was present on the symptomatic cheek than on the normally innervated cheek although both flushed normally; sensation was also reduced in the symptomatic cheek.

DISCUSSION

Vascular response to ocular irritation

The facial nerve lesion blocked the ipsilateral increase in forehead blood flow normally induced by irritating the eye. Parasympathetic fibres emerging from the brainstem with the facial nerve travel to the geniculate ganglion where they branch off in the greater superficial petrosal (GSP) nerve. The GSP nerve unites with the deep petrosal nerve to form the nerve of the pterygoid canal (Vidian nerve). Parasympathetic fibres are relayed to the sphenopalatine ganglion, which distributes postganglionic fibres to the lacrimal gland (Walsh and Hoyt, 1969), intracranial vessels (Walters *et al.*, 1986), and the vascular supply of the nasal mucosa (Lundblad *et al.*, 1983) and facial skin (Lambert *et al.*, 1984).

Gonzalez *et al.* (1975) reported that electrical stimulation of the ophthalmic division of the trigeminal nerve for 2–3 min in cats increased forehead temperature by up to 1 °C. This response lasted 6–8 min. When these experiments were repeated by Lambert *et al.* (1984), most of the response was found to be mediated by a trigeminal-

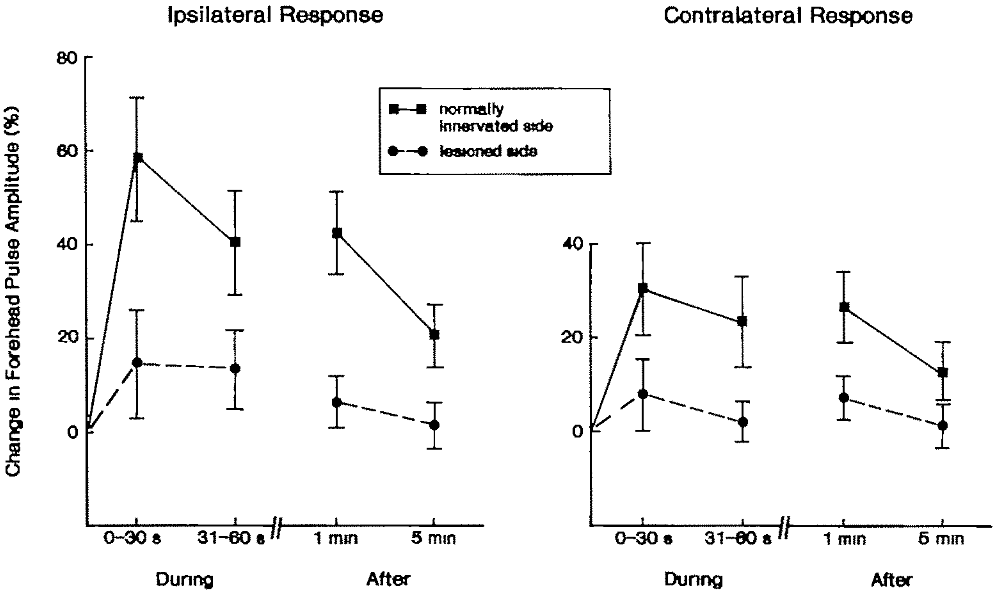

FIG. 3. Vascular responses in the forehead to ocular irritation in patients with a facial nerve lesion. Bars represent the standard error of responses

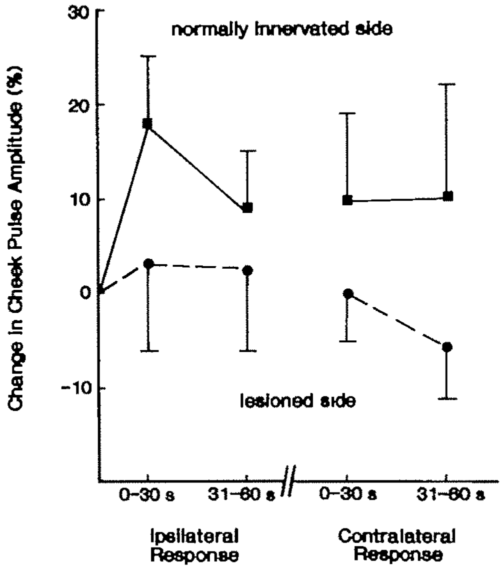

FIG 4. Vascular responses in the cheeks to ocular irritation in patients with a facial nerve lesion. Bars represent the standard error of responses.

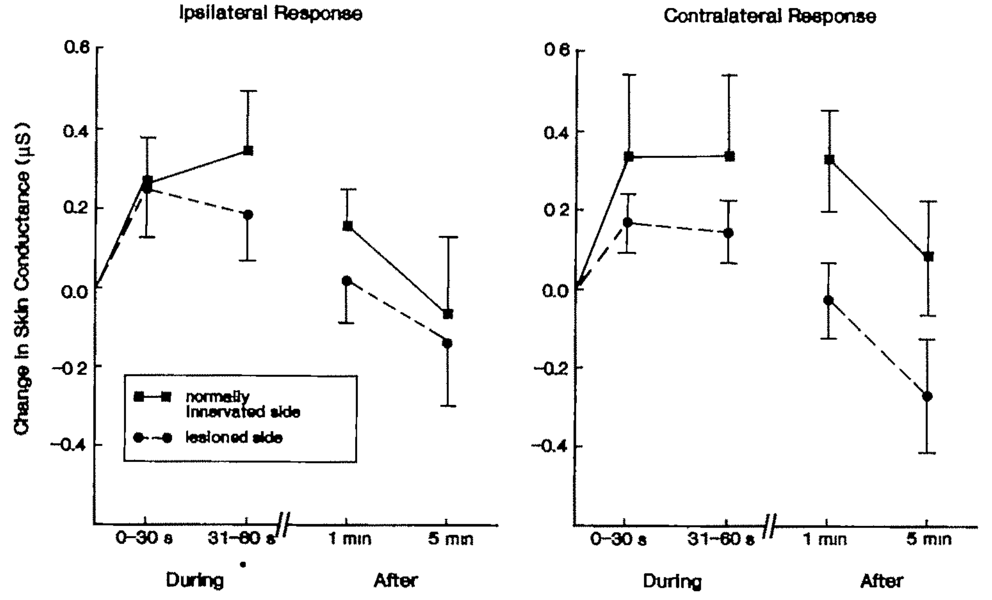

FIG. 5. Electrodermal responses in the forehead to ocular irritation in patients with a facial nerve lesion. The bars represent the standard error of responses.

TABLE 1. THERMOREGULATORY RESPONSES IN PATIENTS WITH A FACIAL NERVE LESION

	Mean response ± SD		
	Lesioned side	*Innervated side*	*t test*
Pulse amplitude (%)			
Forehead	133±73	128±78	0.45
Cheeks	52±61	58±69	0.46
Skin conductance (μS)			
Forehead	2.77±2 14	2.22±1.71	0.84

parasympathetic vasodilator reflex, with the efferent limb in the GSP nerve. The present findings show for the first time in humans that this reflex is active during minor pain induced by ocular irritation. This supports the view that a trigeminal-parasympathetic reflex mediates some of the extracranial vascular changes during headache and facial pain (Lance *et al.*, 1983).

In cats, the trigeminal-parasympathetic reflex employs vasoactive intestinal polypeptide (VIP) as its peripheral neurotransmitter (Goadsby and Macdonald, 1985). The long half-life of VIP (e.g. Lundblad *et al.*, 1983) could explain the persistence of the vascular response after the soap was washed from the eye. The contralateral component of the response could be due to minor crossover of the pathway within the brainstem (Lambert *et al.*, 1984).

Lambert *et al.* (1984) reported that a small proportion of the vascular response to trigeminal stimulation persisted after the trigeminal root had been sectioned, and could have been caused by vasoactive substances released antidromically from sensory nerve endings. Noxious stimulation of the skin produces a local inflammatory response with reddening and wheal formation and a flare in surrounding skin. The flare is mediated by vasoactive substances released from sensory nerve endings near the site of stimulation (Chahl, 1988), probably by an axon reflex which spreads through neighbouring branches of the sensory neuron (Holzer, 1988). Most sensory nerve endings in the cornea and conjunctiva have their cell bodies in the ophthalmic division of the trigeminal ganglion, although the lower eyelid receives fibres from the infraorbital nerve (Williams *et al.*, 1989). Stimulating these nerve endings could produce a flare which spreads to other areas of their receptive field in the forehead and cheeks. However, the absence of response in patients with a facial nerve lesion seems to rule out antidromic activity as an important mediator of the cutaneous response to ocular irritation. Some patients described patchy loss of facial sensation. Nevertheless, the afferent pathway appeared to be grossly intact because all patients reported that the soapy eye drop was at least mildly painful. In fact, pain ratings were greater for the symptomatic eye than for the normally innervated eye, probably because the soap could not be dispersed by blinking or tears.

The vascular response was greater in the forehead than in the cheeks. Thus, irritating end-terminals of the ophthalmic nerve produced a vascular response within their cutaneous distribution. In humans, a flush develops after thermocoagulation of the trigeminal ganglion in the distribution of the division coagulated (Drummond *et al.*, 1983); at least part of this response is mediated by antidromic release of vasoactive substances such as calcitonin gene-related peptide from sensory nerve terminals (Goadsby *et al.*, 1988). Gonzalez *et al.* (1975) reported that stimulating each division of the trigeminal ganglion in cats provoked a rise in temperature which was greater in the cutaneous distribution of that division; furthermore, stimulating discrete points within the brainstem induced increases in facial temperature limited to one trigeminal division. Thus, separate trigeminal-parasympathetic reflexes in each division of the trigeminal nerve might complement antidromic responses. Separate parasympathetic reflexes would be necessary for mediating local vascular responses during lacrimation or salivation.

Nordin (1990) reported that active sympathetic vasodilatation increased blood flow in the forehead skin during body heating, arousal and mental stress. Irritating the eye would be expected to cause arousal but, if present, sympathetic vasodilatation was overshadowed by other influences on cutaneous blood flow. Loss of vasodilatation in denervated skin in patients with facial palsy suggests that most of the response was mediated by a trigeminal-parasympathetic reflex.

Electrodermal response to ocular irritation

In normal subjects electrodermal responses to the soapy eye drop were generally larger on the ipsilateral than contralateral side of the forehead. Nordin (1990) reported that bursts of sympathetic traffic in the supraorbital nerve during body heating preceded phasic increases in electrodermal activity in the forehead lasting a few seconds. In contrast, the soapy eye drop generally induced a gradual increase in skin conductance with only a few phasic peaks during the 60 s of stimulation. Unpublished observations in our laboratory on nine patients undergoing stellate ganglion blockade indicated that the soapy eye drop induced the usual tonic increase in skin conductance on the blocked side of the forehead; thus, the response was not mediated by sympathetic outflow.

Monro (1959) postulated that the face has an additional sudomotor mechanism. In the auriculotemporal syndrome, pathological gustatory sweating develops after parasympathetic fibres occupy denervated postganglionic sympathetic pathways (Gardner and McCubbin, 1956; Glaister *et al.*, 1958). Monro (1959) suggested that parasympathetic fibres in the facial and glossopharyngeal nerves could take this same route during embryonic development to establish rudimentary connections with facial sweat glands. In contrast to sweat glands in the arms and legs (Janowitz and Grossman, 1950), sympathetically denervated facial sweat glands develop supersensitivity to cholinergic agents (List and Peet, 1938; Salvesen *et al.*, 1988, 1989), possibly because of this extra parasympathetic supply. Parasympathetic fibres might also exert an indirect influence on facial sweating. For example, Stevens and Landis (1987) reported that injection of VIP into rats' paws elicited sweating which was blocked by atropine. Thus, release of VIP from parasympathetic fibres during eye pain might induce sweating.

Electrodermal recordings may have been contaminated by electrical activity from the facial muscles or eyes, because small and transient changes could be evoked by voluntarily closing one eye tightly. However, it seems unlikely that paralysis of facial muscles caused the reduction in electrodermal response to the soapy eye drop in patients with a facial nerve lesion, because the reduction persisted for several minutes after the soap had been washed from the eye. Nevertheless, the present findings need to be confirmed using a more direct measure of sweating than electrodermal activity.

Paradoxical lacrimation

In two patients with the longest history of facial paralysis, the previously dry eye now watered more than the normally innervated eye, particularly when the patients were eating. In one of these patients the vascular response to ocular irritation was symmetrical, whereas the electrodermal response was greater on the symptomatic side.

The syndrome of crocodile tears usually develops after injury to the intracranial portion of the facial nerve, and is attributed to cross-regeneration or cross-stimulation of lacrimal and salivary fibres (Boyer and Gardner, 1949; Chorobski, 1951). In the two patients described above lacrimal fibres may have regenerated because tear flow was generally greater on the symptomatic side. Blood-vessels in the forehead may also have been re-innervated in one case. The excessive electrodermal response in this patient suggests that regenerating vascular or lacrimal fibres had made faulty connections with sweat glands; alternatively, sweat glands could have developed denervation supersensitivity.

Thermoregulatory responses in patients with a facial nerve lesion

Facial sweating and flushing in response to body heating were symmetrical in patients with a facial nerve lesion (*cf* List and Peet, 1938). Like thermoregulatory sweating, facial flushing during body heating is mediated by fibres travelling through conventional cervical sympathetic pathways to the face (Drummond and Lance, 1987; Drummond and Finch, 1989; Nordin,1990). Monro (1959) suggested that thermoregulatory sweating in the central mask area of the face could be influenced by outflow through the facial nerve, but this possibility seems remote. The symmetry of thermoregulatory responses in patients with a facial nerve lesion indicates that loss of parasympathetic activity did not increase the effects of sympathetic outflow on the vasculature or sweat glands of the forehead.

Clinical significance of the findings

Painful stimulation of the eye provoked a vascular response in the forehead similar to that observed in some patients during attacks of cluster headache (e.g. fig. 2B, Drummond and Lance, 1984; Drummond and Anthony, 1985). Discharge of the trigeminal nerve during attacks of cluster headache could increase facial blood flow, either by antidromic release of vasoactive agents, or by a trigeminal-parasympathetic reflex.

The electrodermal response to ocular irritation is greatly exaggerated in patients with a postganglionic cervical sympathetic lesion, including patients with cluster headache (Drummond and Lance, 1992). Pathological lacrimal sweating could develop after cross-innervation of sweat glands by parasympathetic fibres (van Weerden *et al.*, 1979). This mechanism could mediate paradoxical sweating in sympathetically denervated areas of the face during attacks of cluster headache (Sjaastad *et al.*, 1981).

The functional importance of the trigeminal-parasympathetic vasodilator reflex in the skin is uncertain. In intracranial vessels, the reflex could protect the blood supply to the brain during inflammatory states, or may play a role in thermoregulation (Walters *et al.*, 1986). When the eye is irritated, blood flow to the lacrimal gland would need to increase to maintain tear flow. The vascular response might spill over to surrounding skin because the lacrimal gland and lower part of the forehead are both supplied by branches of the ophthalmic artery (Williams *et al.*, 1989). The cutaneous response could also help to remove sources of irritation and begin repair.

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PATHOLOGICAL SWEATING AND FLUSHING ACCOMPANYING THE TRIGEMINAL LACRIMAL REFLEX IN PATIENTS WITH CLUSTER HEADACHE AND IN PATIENTS WITH A CONFIRMED SITE OF CERVICAL SYMPATHETIC DEFICIT

EVIDENCE FOR PARASYMPATHETIC CROSS-INNERVATION

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SUMMARY

Electrodermal responses (as a measure of sweating) and vascular responses to irritation of the eye were investigated in 11 cluster headache patients and, for comparison, in another 24 patients with a confirmed site of lesion in the cervical sympathetic pathway. Seven of the cluster headache patients had ocular and thermoregulatory signs of a postganglionic sympathetic lesion. In these patients, and in six of seven patients with a postganglionic sympathetic lesion from some other cause, the electrodermal response to ocular stimulation was far greater on the denervated side of the forehead than on the sympathetically intact side. This pathological response can be explained by lacrimotor fibres branching into vacant sympathetic sudomotor pathways. The response could account for excessive forehead sweating during attacks of cluster headache, in spite of the presence of Horner's syndrome, because parasympathetic outflow to the lacrimal glands increases during attacks.

In patients with diminished sympathetic vasomotor outflow, the vascular response to ocular irritation was also greater on the denervated side of the forehead than on the sympathetically intact side, irrespective of the site of the lesion. The excessive vascular response in sympathetically denervated skin could be caused by adaptive supersensitivity to peptides such as vasoactive intestinal polypeptide, which is known to be released from parasympathetic terminals. The same mechanism might augment vasodilatation during attacks of cluster headache.

INTRODUCTION

A 'trigemino-lacrimal reflex' induces the secretion of tears in response to irritation of structures innervated by the first division of the trigeminal nerve (Walsh and Hoyt, 1969). A similar reflex increases facial blood flow; electrical stimulation of the Gasserian ganglion in cats increases facial temperature by a reflex mediated by trigeminal fibres with the efferent limb in the greater superficial petrosal (GSP) nerve (Lambert *et al.*, 1984). This reflex probably increases lacrimation and facial blood flow during attacks of cluster headache (Gardner *et al.*, 1947; Drummond and Lance, 1984). Antidromic release of vasoactive substances from trigeminal nerve terminals could also contribute to

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vasodilatation (Moskowitz, 1984; Goadsby *et al.*, 1988). The persistent cervical sympathetic deficit (Horner's syndrome) which develops in some patients may be caused by swelling of the internal carotid artery, thus compressing the carotid sympathetic plexus (Kunkle and Anderson, 1961; Nieman and Hurwitz, 1961).

As in other patients with Horner's syndrome, thermally induced sweating is diminished on the symptomatic side of the forehead in patients with cluster headache (Saunte *et al.*, 1983) and yet, during attacks, sweating is greater in this region than in other parts of the face (Sjaastad *et al.*, 1981). Could this paradoxical sweating be caused by trigeminal discharge? Bickford (1938) and Wilkins *et al.* (1938) reported that 1–2 min of painful electrical stimulation of the skin produced sweating in a radius of 3–8 cm around the electrodes. Unlike the situation in cluster headache, this response required intact postganglionic sympathetic fibres. To account for persistence of sweating in the forehead and central mask area of the face after cervical sympathectomy, Monro (1959) suggested that the greater and lesser superficial petrosal nerves contain sudomotor fibres. If so, facial sweating during cluster headache could form part of a trigeminal-GSP nerve reflex.

The aim of our study was to determine whether painful irritation of the eye increased sweating and facial blood flow in patients with cervical sympathetic deficit. If responses were similar to those recorded during attacks of cluster headache, this would suggest that some of the autonomic disturbances in cluster headache are secondary to trigeminal nerve discharge.

METHODS

Subjects

The cluster headache sample fulfilled the criteria of the Headache Classification Committee of the International Headache Society (1988) and comprised 10 males and one female aged between 34 yrs and 69 yrs (mean age 48 yrs). Seven patients were in the active phase of their headache cycle but all patients were studied while headache-free.

For comparison, another 24 patients with a lesion in the cervical sympathetic pathway were also studied. Two females and three males aged between 40 yrs and 75 yrs (mean age 55 yrs) had signs of a central sympathetic lesion after a brainstem stroke. Six males and six females aged between 17 yrs and 67 yrs (mean age 44 yrs) had a preganglionic sympathetic lesion from a transthoracic sympathectomy below the T1 root (seven patients), an operation on the common carotid artery (one patient), removal of a pulmonary lesion (one patient), syringomyelia (one patient), a glioma extending between C7 and T1 (one patient), or a motor vehicle accident involving injury to the chest (one patient). In another five males and two females aged between 47 yrs and 58 yrs (mean age 54 yrs) the sympathetic lesion was probably postganglionic, because the symptomatic pupil dilated weakly or not at all to 2% tyramine eye drops (which releases noradrenaline from sympathetic terminals and thus tests the integrity of postganglionic fibres). The lesion developed after an aneurysm of the internal carotid artery (three patients), migraine (one patient), attempted decompression of the vertebral artery with probable damage to the stellate ganglion (one patient) or Ross' syndrome (one patient) (Drummond and Edis, 1990). The cause of the lesion was unknown in one other patient, but the pattern of autonomic disturbances was consistent with a postganglionic lesion.

Each patient provided informed consent for the procedures, which were approved by the hospital and university ethics committees.

Procedures

Patients were tested in an air-conditioned room maintained at 22 ± 1 °C. The order of the tests depended on the time available and the patient's physical state. Tests done on the same day were separated by 15–30 min to allow responses to return to baseline.

To measure the ocular signs of Horner's syndrome (ptosis and miosis), photographs of the eyes were taken on infrared film using a camera and infrared flash in a photographic chamber (Loewenfeld and Rosskothen, 1974). The patient looked at a black dot attached to an illuminated screen 56 cm from the eyes. Photographs were taken after 30 s of darkness (0.04 lux measured at the position of the subject's eyes with a Mavolux light meter), dim light (2 lux) and bright light (153.3 lux). To measure the rate of pupillary dilatation in darkness, photographs were also taken 5 s after switching off the bright light. To average out random fluctuations in pupil diameter, the various lighting conditions were presented in random order, and two photographs were taken at each light intensity. In 29 patients the photographs were repeated 35 min after placing two drops of 2% tyramine in the conjunctival sac of each eye. Horizontal pupil diameter was later measured from the film negative magnified six times. The distance between the eyelids in darkness, which is influenced by sympathetic tone, was also measured.

To detect changes in skin blood flow, pulse transducers (photoplethysmographs, Grass Instruments Company, Quincy, MA, USA) were attached by adhesive discs to each side of the forehead, 1 cm above the eyebrows and 4 cm from the midline, and to the cheeks, 3 cm below the eyes and 5 cm from the midline. Electrodermal activity was measured from each side of the forehead by passing a 10 μA current between silver-silver chloride electrodes (8 mm internal diameter) attached by adhesive discs 1 cm above the eyebrows and 1 cm and 6 cm from the midline. Electrical interaction between the two channels of electrodermal activity was eliminated by a device which switched between channels 25 times per second so that, at any instant, current passed between only two electrodes.

To induce thermoregulatory sweating and flushing, the seated patient was wrapped in blankets and warmed with air blown under the blankets by a fan heater. Heating continued for 8–63 min (mean 31 min) until facial sweating was visible.

To stimulate facial pain one drop of liquid soap, diluted 1:5 in water, was placed in the conjunctival sac of one eye. After recording facial blood flow and electrodermal activity for 1 min, the soap was washed from the eye with 0.9% saline. Physiological activity was then recorded for 5 min before repeating the procedure with the other eye. In 13 of the 35 patients the eye on the symptomatic side was stimulated first. Patients rated the pain caused by each soapy eye drop on a scale ranging from 1 (extremely mild) to 10 (worst pain imaginable).

The cutaneous vascular response to nitroglycerin was studied in 12 patients with loss of thermoregulatory flushing on one side of the forehead caused by a central sympathetic lesion (three patients), a preganglionic lesion (six patients) or a postganglionic lesion (three patients). Pulse amplitude was recorded from each side of the forehead and cheeks for 5 min after 0.9 mg nitroglycerin was placed under the tongue.

Data reduction

Forehead and cheek pulse amplitudes were measured for 30 s immediately before heating started and at the height of thermoregulatory sweating. Changes in pulse amplitude during body heating were expressed as the percent change from baseline, because the pulse transducer detected only relative changes in blood flow.

Forehead pulse amplitude was measured for 60 s after each soapy eye drop was administered, and 1 min and 5 min after washing the soap from the eye. Responses were expressed as the percent change from the amplitude recorded for 30 s before the first eye drop was instilled.

The electrodermal response to the soapy eye drop was defined as the largest decrease in skin resistance during the next 60 s. Skin conductance is directly proportional to sweating whereas skin resistance is inversely related (Lykken and Venables, 1971); accordingly, skin resistance levels were transformed to conductance units (μS) before calculating the size of the response.

Minute-by-minute changes in pulse amplitude after nitroglycerin was administered were expressed as the percentage change from the pretest level. The maximal increase in pulse amplitude was compared on the denervated and sympathetically intact sides of the forehead ($n = 12$) and cheeks ($n = 7$).

Statistical analyses

Thermoregulatory responses were investigated to confirm that sympathetic vasomotor outflow was diminished on the symptomatic side of the face in individual cases. The pupillary response to tyramine eye drops yielded information about the site of the sympathetic lesion. The presence or absence of ptosis and the asymmetry of thermoregulatory responses and pupillary responses to tyramine eye drops and darkness were examined with paired t tests for groups of patients with a lesion at a similar site. Responses in patients with cluster headache were studied separately, to determine whether sympathetic activity was diminished on the symptomatic side of the face and, if so, to identify the site of the lesion.

Vascular and electrodermal responses to eye pain were investigated with analyses of variance (MANOVA programme, SPSSX). Responses in six patients with cluster headache and signs of a postganglionic sympathetic lesion were compared with responses in six patients with a postganglionic lesion from some other cause. An additional orthogonal contrast was computed between responses in 13 patients with a preganglionic or central sympathetic lesion, and responses in 12 patients with a postganglionic lesion (including the six cluster headache patients). Each analysis had repeated measures factors for laterality (denervated versus sympathetically intact side of the forehead) and stimulation (the stimulated side versus the contralateral side). Significant interactions between factors were investigated at each level of the factor to identify the source of the interaction. Four cluster headache patients and four others who showed symmetrical thermoregulatory responses in the forehead were not included in these analyses and their results are reported separately. In addition, one patient with cluster headaches and signs of a postganglionic sympathetic lesion was excluded because her responses were several times larger than responses in any other patient, and thus distorted the estimation of mean values and variance of responses. A patient with a central sympathetic lesion was excluded because he had lost sensation on the symptomatic side of his face after a stroke so that irritating the eye was not an adequate stimulus.

The maximal increase in pulse amplitude after administration of nitroglycerin was compared on the sympathetically intact and denervated sides of the face with paired *t* tests. Patient numbers were too small to investigate the response in relation to the site of the sympathetic lesion.

RESULTS

Ocular features of Horner's syndrome

Group 1: patients without cluster headache

Central lesion. Each patient had miosis and ptosis on the symptomatic side. Dilatation of the affected pupil to 2% tyramine eye drops exceeded the contralateral response in four patients, so that miosis was abolished (Table 1). Another patient with a history of a brainstem stroke was not tested because of glaucoma.

Preganglionic lesion. Only one of seven patients with a preganglionic sympathectomy had significant ptosis on the operated side (Table 1), and none had miosis. In the five patients with a preganglionic lesion from some other cause, miosis and ptosis were present

TABLE 1 OCULAR SYMPATHETIC DISTURBANCES

	Ptosis (mm)		*Pupillary asymmetry (mm)***				*Increase in diameter after tyramine (mm)*	
			After 5 s darkness		*After tyramine (mm)*			
	n > 0.5 mm	*Mean ±SE*	*n > 0.5 mm*	*Mean ±SE*	*n > 1.0 mm*	*Mean ±SE*	*Intact side*	*Denervated side*
Site of sympathetic lesion								
Central	4/5	1.0±0.3*	3/5	0.7±0.2*	0/4	−0.4±0.3	1.4±0.9	2.2±1.0
Preganglionic								
Sympathectomy	1/7	−0.1±0.2	0/7	0.0±0.1	0/3	0.1±0.3	1.8±0.8	1.7±0.7
Others	1/5	0.4±0.1*	3/5	0.8±0.2*	0/4	0.2±0.1	2.8±0.3	3.0±0.4
Postganglionic	6/7	1.1±0.3*	5/7	1.1±0.3*	6/7	2.6±0.6*	2.8±0.3	0.7±0.3*
Cluster headache								
Sympathetic lesion	0/7	0.1±0.1	5/7	0.7±0.1*	7/7	2.5±0.4*	2.5±0.4	0.4±0.3*
Others	0/4	−0.2±0.3	1/4	0.3±0.2	0/4	−0.4±0.5	2.2±0.9	2.6±0.5

*Difference between sides statistically significant, $P < 0.05$ **Difference in diameter between the non-symptomatic and symptomatic pupils; pupil diameter after tyramine eye drops was measured in bright light (153.5 lux) to a variable extent. In four of these patients, pupillary dilatation after 2% tyramine eye drops abolished miosis (Table 1). A patient with syringomyelia was not tested with tyramine eye drops but, nevertheless, was thought to have a preganglionic sympathetic lesion as part of his condition.

Postganglionic lesion. Six of seven patients had significant ptosis on the symptomatic side (Table 1), and miosis was present to some extent in all seven patients. Pupillary dilatation to 2% tyramine eye drops was diminished or absent on the symptomatic side in each case. In three patients with an aneurysm of the internal carotid artery and one with migraine, the symptomatic pupil dilated less than 0.5 mm after tyramine eye drops were instilled. In the other three patients the symptomatic pupil dilated between 1 mm and 2 mm. In the patient with Ross' syndrome, pupil asymmetry after tyramine eye drops averaged only 0.9 mm, possibly because of an increase in intrinsic contractility of iris muscles, or because the lesion spared some ocular sympathetic fibres. The sympathetically denervated pupil dilated 2 mm whereas the other pupil dilated 2.4 mm.

Group 2: patients with cluster headache

Seven of 11 patients had clear ocular signs of a persistent postganglionic sympathetic lesion. The symptomatic pupil dilated more slowly in darkness than the other pupil, and was unresponsive (four patients) or dilated less than the contralateral pupil to tyramine eye drops (Table 1). In two of the four remaining patients the pupil on the affected side dilated slowly in darkness but both pupils dilated to tyramine eye drops. Sympathetic activity appeared to be normal on the habitually affected side of the face in another case, although the patient had noticed miosis and ptosis during attacks. The response to tyramine eye drops was unexpectedly impaired on the headache-free side in another patient. This patient had no past history of contralateral headaches, nor of miosis or ptosis during attacks.

There was no clear relationship between the frequency or duration of attacks and the presence or absence of a persistent postganglionic sympathetic lesion in the group as a whole. Unlike patients in Group 1, ptosis greater than 0.5 mm was not observed in any of the cluster headache patients (Table 1).

Thermoregulation

Group 1: patients without cluster headache

Central lesion. Vasodilatation (Table 2) and sweating during body heating were diminished on the symptomatic side of the forehead in three of five patients. Thermoregulatory responses were symmetrical in the other two patients, although the ocular signs of Horner's syndrome were present in each case.

Preganglionic lesion. Thermally induced increases in forehead and cheek pulse amplitude were smaller on the symptomatic side in seven patients with a surgical lesion of the sympathetic chain below the first thoracic root (Table 2). Hemifacial loss of sweating was observed in each case. A similar thermoregulatory disturbance was observed in four of five patients with a probable preganglionic sympathetic lesion from some other cause. The only exception was a man with a glioma extending down to the first thoracic segment, who showed the ocular signs of Horner's syndrome without any thermoregulatory disturbance in the face.

TABLE 2 CHANGE IN FACIAL BLOOD FLOW DURING BODY HEATING

	Mean increase ±SE (%)				*Difference between sides*			
	Forehead		*Cheeks*		*Forehead*		*Cheeks*	
	Denervated side	*Intact side*	*Denervated side*	*Intact side*	*n > 20%*	*Mean ±SE (%)*	*n > 20%*	*Mean ±SE (%)*
Site of sympathetic lesion								
Central	105±57	139±48	114±71	336±141	3/5	34±17	2/3	122±78
Preganglionic								
Sympathectomy	1±9	142±21*	40±46	142±81*	7/7	141±22*	7/7	102±36*
Others	10±28	182±50	70±30	129±79	4/5	171±72	1/2	59±49
Postganglionic								
Before bifurcation	170±30	292±135	212±81	395±172	1/2	122±165	2/2	183±91
After bifurcation	34±25	77±23*	7±11	2±11	5/5	43±12*	0/5	−5±8
Cluster headache								
Sympathetic lesion	18±15	102±18*	21±9	63±21	7/7	84±22*	4/6	42±17
Others	70±10	50±23	31±10	4±7	0/4	−20±20	0/4	−27±12

*Difference between sides statistically significant, $P < 0.05$

Postganglionic lesion. Increases in pulse amplitude and sweating during body heating were smaller on the symptomatic side of the forehead than on the other side, except in a woman whose Horner's syndrome developed after a difficult operation on the base of the neck. Vasodilatation in the symptomatic cheek was also diminished in two patients with a lesion close to the superior cervical ganglion. In patients with a postganglionic lesion distal to the bifurcation of the common carotid artery (caused by an internal carotid aneurysm in three cases and migraine in one), cheek pulse amplitude increased (two patients) or decreased symmetrically (two patients).

Group 2: patients with cluster headache

Thermally induced increases in pulse amplitude (Table 2) and sweating were reduced or absent on the symptomatic side of the forehead in the seven patients with ocular signs of a postganglionic sympathetic lesion. Furthermore, increases in pulse amplitude recorded from the symptomatic cheek were at least 20% smaller than on the headache-free side in four of six patients (Table 2).

In the four patients with little evidence of postganglionic ocular sympathetic deficit on the symptomatic side of the face, thermoregulatory responses were symmetrical or, in one case, greater on the side affected by headaches (noteably the patient with greater pupillary dilatation to tyramine eye drops on this side).

Ocular irritation

Pain ratings

Ratings of the pain produced by the soapy eye drop averaged 5 (moderately painful) on the symptomatic side and 4.5 on the sympathetically intact side (difference not statistically significant). Ratings were lower in 11 patients with cluster headache than in the 24 patients in Group 1 [mean ratings 3.7 and 5.2, respectively, $F(1,33) = 6.38$, $P < 0.05$]. There was no significant relationship between pain ratings and the size of vascular or electrodermal responses on either side of the forehead.

Electrodermal and vascular responses

The skin conductance level immediately before the first eye drop was similar on the denervated and sympathetically intact sides of the forehead in all groups of patients. Shortly after the soapy eye drop was administered, electrodermal activity (Fig. 1) and pulse amplitude (Fig. 2) generally increased on the ipsilateral side of the forehead. A small response also occurred on the other side of the forehead. The size of these responses depended on the site of the sympathetic lesion (*see below*). Statistical analyses confirmed that the electrodermal response during ocular stimulation was greater on the ipsilateral side of the forehead than on the contralateral side [F(1,21) = 17.35, $P < 0.001$], as was the increase in pulse amplitude [F(1,22) = 18.27, $P < 0.001$]. The ipsilateral vascular response persisted 1 min and 5 min after the soap was washed from the eye [F(1,22) = 15.40, $P < 0.001$ and F(1,22) = 18.06, $P < 0.001$, respectively], more so on the denervated side of the forehead (Fig. 2). In patients in Groups 1 and 2 with a vasomotor lesion anywhere in the cervical sympathetic pathway, increases in pulse amplitude were greater on the denervated side of the forehead than on the intact side both during (Fig. 2A) and after (Fig. 2B,C) ipsilateral ocular stimulation [F(1,22) = 8.05

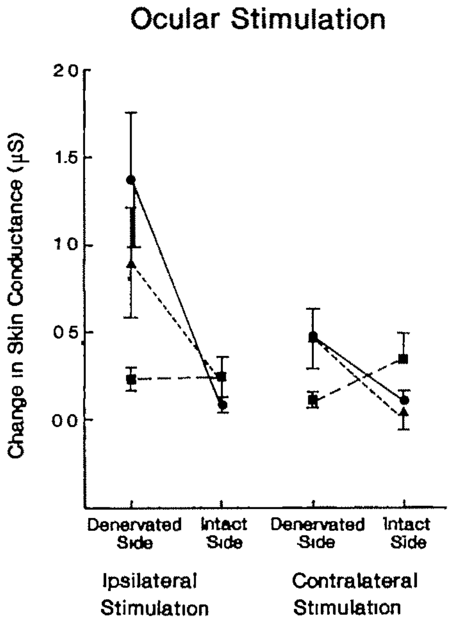

FIG. 1. Maximal changes in skin conductance on the denervated and sympathetically intact sides of the forehead while irritating the eye with soapy water. ●, cluster headache (n = 6), ▲, postganglionic lesion (n = 6); ■, preganglionic or central lesion (n = 12). Bars represent the standard error of responses. Increases in skin conductance were greater on the denervated side of the forehead in patients with a postganglionic sympathetic lesion (including cluster headache) than in patients with a preganglionic or central lesion. One cluster headache patient with ocular signs of a postganglionic sympathetic lesion was excluded from this analysis because of outlying responses; stimulating the symptomatic eye caused an increase in skin conductance of 7.25 µS on the denervated side of the forehead, and 3.43 µS on the other side. During stimulation of the non-symptomatic eye, skin conductance increased 7 07 µS, compared with 5.24 µS on the denervated side of the forehead.

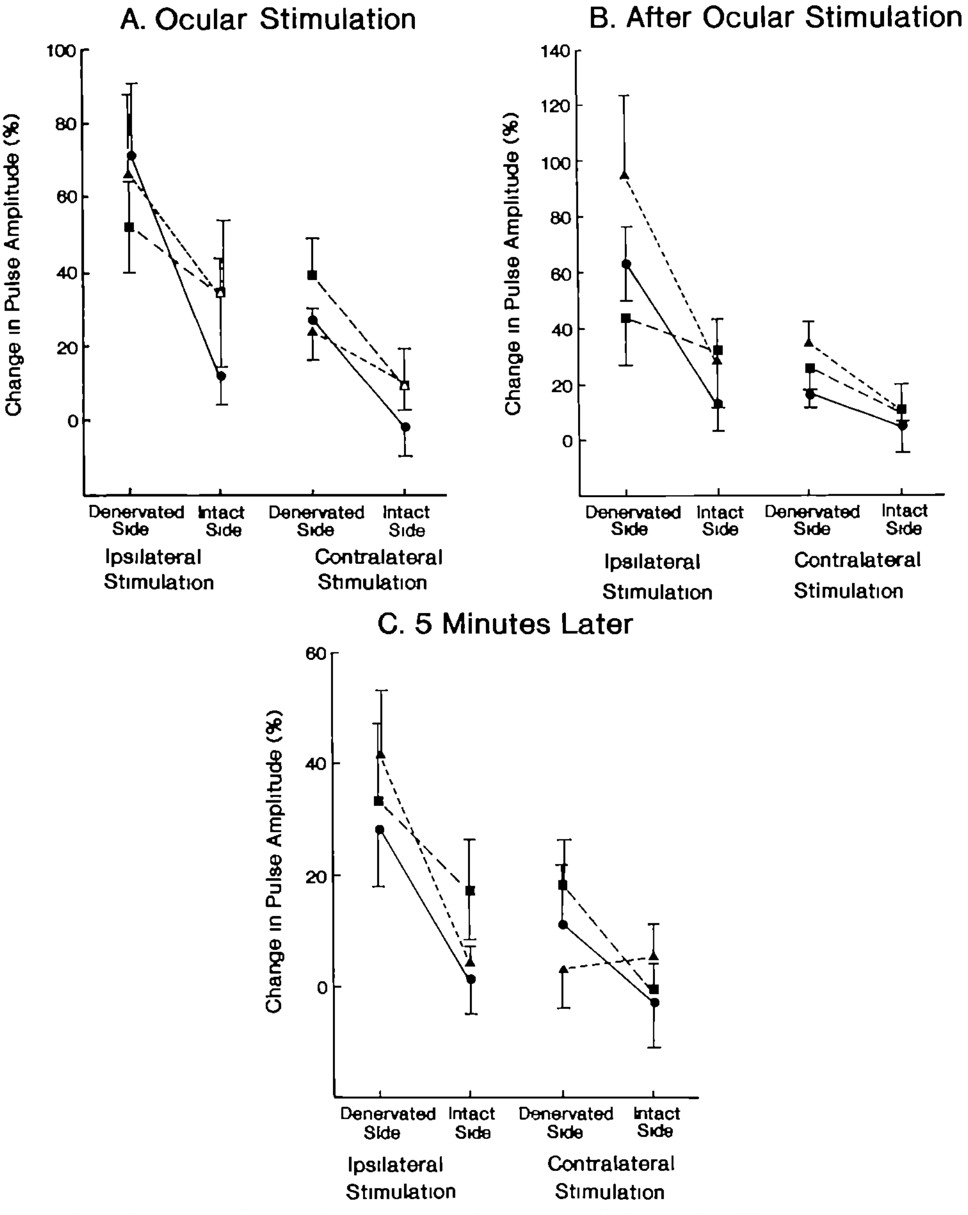

FIG. 2 Change in pulse amplitude on the denervated and sympathetically intact sides of the forehead after irritating the eye with soapy water. ●, cluster headache ($n = 6$); ▲, postganglionic lesion ($n = 6$); ■, preganglionic or central lesion ($n = 12$) Bars represent the standard error of responses. A, during ipsilateral and contralateral stimulation, increases in pulse amplitude were larger on the denervated side of the forehead than on the sympathetically intact side. B, one minute after stimulation, the response was greater in patients with a postganglionic sympathetic lesion (including cluster headache) than in patients with a preganglionic or central lesion. C, the response persisted on the denervated side of the forehead 5 min after the soapy water had been washed from the eye In the cluster headache patient excluded from analyses because of outlying responses, pulse amplitude increased 656% and 367%, respectively, on the symptomatic and headache-free sides of the forehead during stimulation of the symptomatic eye. Five minutes after stimulation, pulse amplitude was still more than three times greater than baseline on the symptomatic side of the forehead Irritating the non-symptomatic eye provoked increases of 408% on the non-symptomatic side of the forehead and 267% on the symptomatic side.

to 27.15, $P < 0.01$], and even during contralateral stimulation [F(1,22) = 12.52, $P < 0.01$] (Fig. 2A).

Four patients in Group 1 with a confirmed site of lesion had ocular signs of Horner's syndrome but symmetrical thermoregulatory responses. Neither vascular nor electrodermal responses to ocular stimulation differed greatly between the two sides of the forehead in any of these patients.

Patients in Group 1 with a central or preganglionic lesion

Vascular responses were greater on the sympathetically denervated side in patients with a central or preganglionic lesion (Fig. 2), whereas electrodermal responses generally were symmetrical. However, the electrodermal response was clearly greater on the denervated side of the forehead in one of 11 patients with a preganglionic sympathetic lesion (0.71 μS and 0.02 μS, respectively, when the ipsilateral eye was stimulated), and smaller on the denervated side by at least 0.7 μS in three others.

Stimulating the symptomatic eye of the patient with hemifacial loss of sensation induced virtually no vascular or electrodermal response. In contrast, stimulating the other eye caused pulse amplitude to increase 30% on the ipsilateral side of the forehead. Skin conductance did not change on either side of the forehead when the non-symptomatic eye was stimulated.

Patients in Group 1 with a postganglionic lesion and patients in Group 2 with cluster headache

The electrodermal response was greatly exaggerated on the denervated side of the forehead for patients in Groups 1 and 2 with thermoregulatory and ocular signs of a postganglionic sympathetic lesion (Figs 1, 3). Neither electrodermal nor vascular responses differed significantly between patients with cluster headache and those with a postganglionic lesion from some other cause. Statistical analyses confirmed that the electrodermal response was greater than in patients with a preganglionic or central sympathetic lesion [mean response 1.12 μS versus 0.22 μS, F(1,21) = 14.78, $P < 0.001$] (Fig. 1), as was the increase in pulse amplitude [after stimulation, F(1,22) = 5.47, $P < 0.05$] (Fig. 2B). Even when the opposite eye was stimulated, the electrodermal response on the denervated side of the forehead was larger than the ipsilateral response in these patients [0.46 μS versus 0.17 μS, $t(11) = 2.29$, $P < 0.05$], and was larger than the response in patients with a more centrally placed lesion [mean response on the denervated side 0.46 μS versus 0.10 μS, F(1,21) = 9.08, $P < 0.01$] (Fig. 1).

One patient in Group 1 with ocular and thermoregulatory signs of a postganglionic lesion initially showed a symmetrical response to the soapy eye drop. After further ocular irritation with ammonia and onion fumes, which induced slightly larger electrodermal responses on the denervated side of the forehead than on the other side, the symptomatic eye was again irritated with soapy water. On this occasion electrodermal activity increased 1.84 μS, considerably larger than responses of 0.21 μS recorded previously from the denervated side of the forehead, and 0.28 μS recorded from the sympathetically intact side. Thus, repeated stimulation may have brought sweat glands closer to their response threshold.

Four patients in Group 2 had little evidence of a postganglionic sympathetic lesion on the side affected by cluster headaches. Unlike other cluster headache patients, vascular

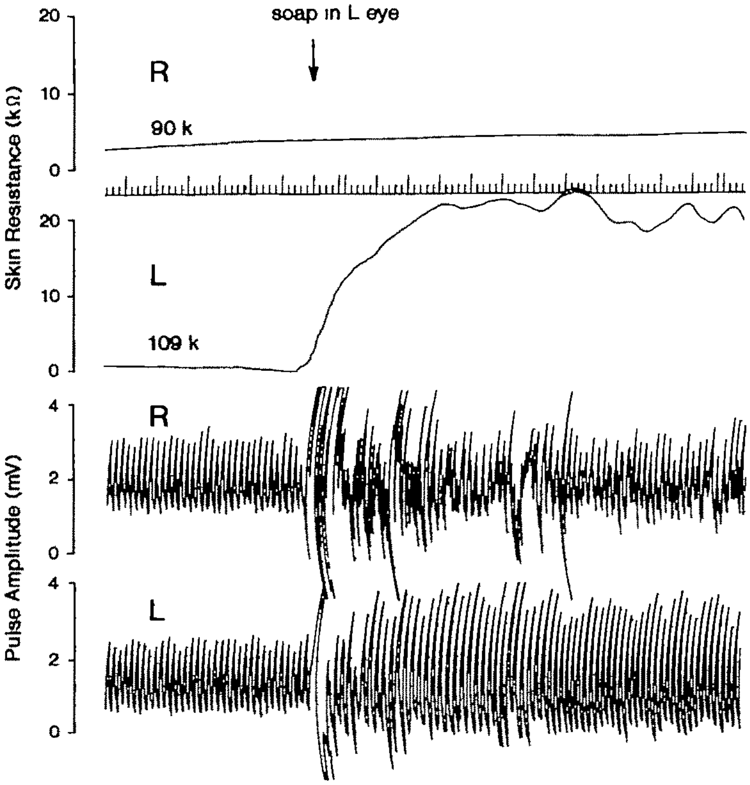

FIG. 3. Electrodermal and vascular responses to stimulation of the left eye with soapy water in a patient with left-sided cluster headaches and signs of a postganglionic cervical sympathetic lesion. Irregularities in pulse amplitude when the eye drop was administered were caused by movements of the face. The timing channel, between the two skin resistance channels, shows intervals of 1 s (small spikes), 5 s (large spikes) and 60 s (large double-spikes).

responses to the soapy eye drop were similar on both sides of the forehead and electrodermal responses were minimal on the symptomatic side. It was interesting to note that the electrodermal response to ocular stimulation was greater on the headache-free side of the patient with ocular and thermoregulatory signs of a postganglionic lesion on this side (0.50 μS compared with 0.15 μS on the side affected by cluster headaches).

Vascular response to nitroglycerin

Pulse amplitude increased significantly on each side of the forehead for 3 min after the drug was administered. Maximal increases in pulse amplitude were similar on the denervated and sympathetically intact sides of the forehead (41% and 55%, respectively) and cheek (37% and 36%, respectively), the differences not being statistically significant.

DISCUSSION

Sympathetic pathway to the face

Vasodilator fibres in the cervical sympathetic pathway mediate increases in facial blood flow during heat stress (Drummond and Lance, 1987; Drummond and Finch, 1989; Nordin, 1990). These fibres appear to take the same course as sudomotor fibres, leaving the spinal cord below the first thoracic root (Morris *et al.*, 1984; Drummond and Lance, 1987). In our previous study, thermally induced vasodilatation was diminished on the symptomatic side of the forehead in 20 of 21 patients with a lesion in the cervical sympathetic pathway (Drummond and Lance, 1987). The exception was a patient with a brachial plexus injury affecting only the first thoracic root. In the present study, thermally induced responses were diminished on the symptomatic side of the forehead in 20 of 24 patients in Group 1 with a confirmed site of lesion in the cervical sympathetic pathway. Inspection of the face indicated that areas which did not flush corresponded closely with areas which did not sweat.

One of the patients in Group 1 had developed ocular signs of Horner's syndrome during an attack of systemic lupus erythematosus; these signs were attributed to brainstem ischaemia although a computerized tomography scan was normal. At the time of testing, 5 mths after systemic symptoms had resolved, an ocular Horner's syndrome remained on one side but thermoregulatory responses were symmetrical. To account for normal facial sweating in patients with ocular signs of a central sympathetic lesion, Nathan and Smith (1986) suggested that sudomotor and ocular sympathetic fibres follow slightly different paths in the brainstem.

In our previous study, hemifacial loss of sweating and vasodilatation was observed in two patients who had undergone surgical resection of sympathetic roots between T2 and T4 (Drummond and Lance, 1987). Ocular sympathetic activity was normal in each case. We now report similar findings in another seven patients, confirming that most ocular sympathetic fibres leave the spinal cord above T2 (Goetz, 1948). The converse result was obtained in a patient with a glioma extending down the spinal cord to the first thoracic region, which spared vasomotor and sudomotor fibres originating below that level but damaged ocular sympathetic fibres derived from the T1 segment.

Two other patients in Group 1 with ocular signs of Horner's syndrome but symmetrical thermoregulatory responses had been studied 5 yrs previously. In both cases, thermally induced sweating and vasodilatation had been diminished on the symptomatic side of the forehead at the first examination. Thus, function had recovered during the 5 yrs between tests. In one case the return of function was patchy, because thermally induced increases in blood flow were diminished in the symptomatic cheek.

Vasodilatation in the symptomatic cheek during body heating was diminished in 12 of 14 patients in Group 1 with a sympathetic lesion proximal to the bifurcation of the common carotid artery (Table 2). In contrast, this response was symmetrical or absent in both cheeks of patients with an intracranial lesion distal to the bifurcation. List and Peet (1938) and Morris *et al.* (1984) concluded that sudomotor fibres to the cheeks follow branches of the external carotid artery, whereas those to the forehead travel intracranially with the internal carotid artery. Vasomotor fibres to the forehead and cheeks also appear to separate at the carotid bifurcation.

Site of the sympathetic lesion in cluster headache

As in our previous studies (Lance and Drummond, 1987; Drummond, 1988*a*), autonomic disturbances persisting between attacks of cluster headache closely resembled those caused by a postganglionic lesion in the cervical sympathetic pathway. In particular, the response of the symptomatic pupil to tyramine eye drops was reduced in cluster headache patients with ocular signs of Horner's syndrome, and in Group 1 patients with a postganglionic sympathetic lesion from some other cause. However, the lesion was not identical in these two groups, because ptosis was absent in cluster headache patients. Ptosis which develops during attacks of cluster headache usually resolves when the attack subsides (Drummond, 1988*b*), indicating that the lesion in the carotid arterial wall is milder and partly reversible in patients with cluster headache.

Our results confirmed that thermally induced vasodilatation and sweating were diminished on the symptomatic side of the forehead in cluster headache patients with ocular signs of Horner's syndrome (Saunte *et al.*, 1983; Lance and Drummond, 1987). Ekbom and Greitz (1970) reported that constriction of the lumen of the internal carotid artery in the cavernous sinus during an attack of cluster headache spread down the carotid canal later in the attack. The angiographic appearance of the vessel was attributed to swelling of the arterial wall, a process which could damage surrounding sympathetic fibres. It seems unlikely that the lesion would extend down to the bifurcation of the common carotid artery and affect vasomotor fibres distributed to the cheeks; nevertheless, thermally induced flushing of the symptomatic cheek was diminished in some patients. A second lesion could possibly involve fibres travelling with the external carotid artery, but there is no evidence for this at present.

Response to ocular stimulation

Although the size of electrodermal or vascular responses to ocular stimulation was not related to subjective ratings of pain, nociceptive fibres in the trigeminal nerve almost certainly form the afferent limb of a reflex mediating lacrimation, vasodilatation and sweating. Consistent with this view, no response was detected in the patient with a central lesion affecting facial sensation. Pain ratings by cluster headache patients were smaller than ratings by other patients, possibly because the eye pain was rated in relation to the intense pain of their attacks.

Studies in our laboratory have shown that vascular and sweating responses to ocular irritation were greatly diminished or absent on the denervated side of the forehead in patients with a facial nerve lesion compromising parasympathetic outflow through the GSP nerve (Drummond, 1992). These findings suggest that the GSP nerve normally mediates the local autonomic response to ocular irritation.

Pathological lacrimal sweating. The major finding of our study was the dramatic electrodermal response to ocular stimulation on the denervated side of the forehead in patients in Groups 1 and 2 with a postganglionic sympathetic lesion. To our knowledge, sweating of the forehead in response to ocular stimulation has been described in only one other patient with Horner's syndrome (van Weerden *et al.*, 1979). This patient had a 3-yr history of continuous mild pain over the right eye and temple. Sweating on the right side of the forehead was first noticed 6 mths after the onset of headache. The presence of an ocular sympathetic lesion on the right side was confirmed by the lack of pupillary dilatation to 4% cocaine eye drops. Schirmer's test showed lacrimation to be normal on both sides; however, the test itself provoked profuse sweating in the right frontal region, presumably because of conjunctival irritation. Van Weerden *et al.* (1979) suggested that lacrimal fibres had sprouted into vacant sympathetic sudomotor pathways to the forehead, so that stimuli which normally induced lacrimation also provoked sweating.

Parasympathetic fibres to the lacrimal glands leave the brainstem in the nervus intermedius, branch off in the GSP nerve, and are joined by sympathetic fibres from the internal carotid nerve plexus (deep petrosal nerve) to form the nerve of the pterygoid canal (Vidian nerve) before synapsing in the sphenopalatine ganglion (Fig. 4). Postganglionic lacrimal fibres then leave in orbital rami, some of which loop back to

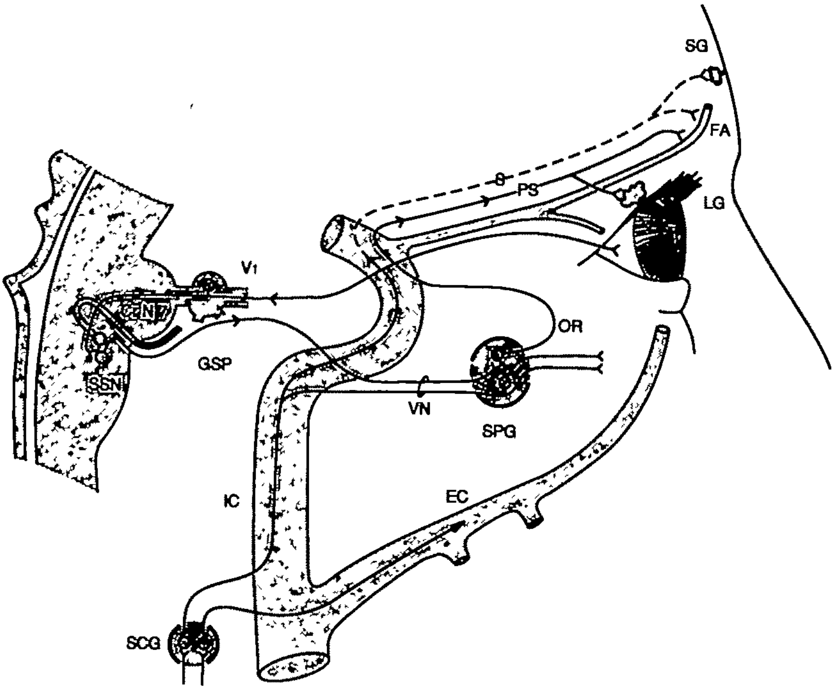

FIG. 4. Postulated explanation for forehead flushing and sweating associated with the ocular Horner's syndrome of cluster headache and other postganglionic sympathetic lesions Sympathetic fibres (S) arising from the superior cervical ganglion (SCG) are compromised in the wall of the internal carotid artery (IC), causing their peripheral distribution to the frontal arteries (FA) and sweat glands (SG) to degenerate. Parasympathetic fibres (PS), originating in the superior salivatory nucleus (SSN), traverse the facial nerve (CrN7) and the greater superficial petrosal nerve (GSP) to join the Vidian nerve (VN) and synapse in the sphenopalatine ganglion (SPG); postganglionic fibres then loop back as orbital rami (OR) to the cavernous sinus and internal carotid artery where they form a retro-orbital plexus with sympathetic and trigeminal fibres, before advancing to supply the lacrimal glands (LG) and cutaneous circulation of the forehead. Conjunctival irritation stimulates afferent fibres in the first division of the trigeminal nerve (V_1), which reflexly activates parasympathetic outflow to the lacrimal glands and forehead circulation. The interrupted line represents the route taken by parasympathetic fibres that occupy the denervated sympathetic pathway and cause frontal sweating and flushing in response to the conjunctival stimulus. EC = external carotid artery.

the cavernous sinus where they form a retro-orbital plexus with sympathetic fibres from the internal carotid nerve and filaments from the ophthalmic and maxillary branches of the trigeminal nerve (Ruskell, 1970; Ruskell and Simons, 1987). The close proximity of sympathetic and parasympathetic fibres in the cavernous sinus and Vidian nerve provides ideal conditions for aberrant re-innervation after injury to postganglionic sympathetic fibres (Fig. 4).

After preganglionic sympathectomy, fibres originally mediating salivation, or vascular changes associated with salivation, are thought to cause pathological gustatory sweating by re-innervating sudomotor neurons in the superior cervical ganglion (Kurchin *et al.*, 1977). A similar mechanism could account for pathological lacrimal sweating in the patient in Group 1 who had undergone preganglionic resection of sympathetic roots between T2 and T4.

Mechanisms such as adaptive supersensitivity could contribute to pathological lacrimal sweating. Salvesen *et al.* (1987) investigated the sweating response to subcutaneous injection of pilocarpine 0.1 mg/kg body weight in four patients with a central sympathetic lesion and in three patients with Horner's syndrome after a brachial plexus injury. Similar studies were later carried out in two patients with a probable postganglionic sympathetic lesion (Salvesen *et al.*, 1989). Two patients with a central lesion and one patient with a postganglionic lesion sweated more on the denervated side of the forehead than on the sympathetically intact side after the pilocarpine injection. Loss of thermally induced sweating on the symptomatic side of the forehead was confirmed in each case. Thus, facial sweat glands may develop supersensitivity after injury to cervical sympathetic fibres. Nevertheless, supersensitivity could not be the only requirement for pathological lacrimal sweating, because patients in Group 1 with a central sympathetic lesion showed a normal electrodermal response to the soapy eye drop.

Vascular response to ocular irritation. The vascular response to trigeminal stimulation is mediated by a trigeminal-GSP nerve vasodilator reflex which, in cats, employs vasoactive intestinal polypeptide (VIP) as its peripheral neurotransmitter (Goadsby and Macdonald, 1985). The persistence of the vascular response for several minutes after washing the soap from the eye is consistent with the release of a long-acting vasodilator such as VIP. A small part of the vascular response to trigeminal stimulation may be mediated by antidromic release of neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) from trigeminal nerve terminals (Lambert *et al.*, 1984). In humans, the local flush which develops after thermocoagulation of a division of the trigeminal ganglion (Drummond *et al.*, 1983) is associated with the release of CGRP (Goadsby *et al.*, 1988). Antidromic responses are confined to the receptive field of the involved neurons; thus, it is not surprising that an antidromic response to ocular stimulation was absent in the forehead of our patient with a central sympathetic lesion and loss of facial sensation.

The vascular response to ocular stimulation was greater on the denervated side of the forehead than on the sympathetically intact side in all groups of patients. In contrast, unpublished observations in our laboratory have shown that unilateral stellate ganglion blockade does not increase the vascular response. The response to nitroglycerin, which relaxes smooth muscle by a non-neural mechanism, was similar on the denervated and sympathetically intact sides of the face in the present series of patients. Hence, a change in intrinsic contractility of denervated smooth muscle does not account for the increased response to ocular stimulation. Vascular tone increases during the days and weeks after cervical sympathectomy (Lewis and Landis, 1930), possibly because of non-specific adaptive supersensitivity (Fleming and Westfall, 1988). The neurotransmitter mediating pathological lacrimal flushing has not been established, but VIP is a likely contender because it is co-localized with acetylcholine in parasympathetic fibres innervating cranial blood vessels and exocrine glands (Lundberg, 1981; Edvinsson *et al.*, 1988). Over the course of time, sympathetically denervated blood vessels may become supersensitive to VIP or to other neuropeptides released by parasympathetic or sensory fibres (antidromically as an axon reflex) during ocular irritation.

After injury to pre- or postganglionic sympathetic fibres, gustatory stimuli induce vasodilatation as well as sweating in sympathetically denervated parts of the face (Uprus *et al.*, 1934; Drummond and Lance, 1987; Drummond *et al.*, 1987), presumably because of aberrant re-innervation in vasomotor pathways. A similar mechanism could mediate the heightened vascular response to ocular stimulation on the denervated side of the forehead in patients with a postganglionic sympathetic lesion.

Pathological lacrimal sweating and vasodilatation in cluster headache. Sweating and vascular responses to ocular irritation were greatly exaggerated in patients with signs of a postganglionic sympathetic lesion on the side affected by cluster headaches. The mechanism suggested above for pathological lacrimal sweating could therefore induce excessive sweating on the painful side of the forehead during attacks of cluster headache (Fig. 4). Denervation supersensitivity of facial sweat glands, which is a feature of cluster headache (Saunte *et al.*, 1983; Salvesen *et al.*, 1988), could also increase sweating during attacks.

The presence of small responses on the side contralateral to trigeminal stimulation indicates some crossover of the reflex pathway within the brainstem (Lambert *et al.*, 1984). The contralateral component of the response was greatly exaggerated in patients in Groups 1 and 2 with a postganglionic sympathetic lesion; stimulating the normal eye provoked pathological lacrimal sweating in sympathetically denervated skin. Sjaastad *et al.* (1987) reported that forehead sweating during attacks persisted on the original side of cluster headaches in a patient whose attacks had changed sides after 10 yrs, but who still had signs of a postganglionic sympathetic lesion on the original side of headaches. Thus, sweating during attacks could have been provoked by contralateral trigeminal nerve activity. One of our patients with cluster headache had signs of a postganglionic sympathetic lesion and pathological lacrimal sweating on the headache-free side. In this patient, and in another reported by Sjaastad *et al.* (1988), the sympathetic lesion was probably not caused by cluster headaches but, nevertheless, could have influenced the pattern of autonomic disturbances during attacks.

In conclusion, our findings strengthen the view that a lesion in or around the cavernous sinus causes an ocular Horner's syndrome in cluster headache, and impairment of thermoregulatory sweating and vasodilatation on the symptomatic side of the forehead. The paradoxical sweating and vasodilatation observed in this area during some attacks of cluster headache can be explained by reflex activation of parasympathetic fibres which have grown into vacant sympathetic pathways. Conversely, autonomic disturbances could contribute to the perception of pain. For example, vasodilatation and oedema in the cavernous sinus could produce pain by compressing sensory nerves and aggravating local neurogenic inflammation (Hardebo, 1991).

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PROCESSING OF SPATIAL CONTRAST IN PERIPHERAL VISION IN PARKINSON'S DISEASE

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SUMMARY

Two experiments were carried out to test the hypothesis, based on anatomical evidence, that contrast gain might be reduced in the retinal periphery in Parkinson's disease. In the first experiment, subjects set contrast thresholds before and after adaptation to a vertical grating of 2 cycles per degree (c/deg), either stationary or oscillating sideways through its spatial period at 8 Hz, presented either in central vision or 7 degrees peripherally. Threshold elevations were similar for central viewing in both patients and controls. However, for peripheral viewing, elevations were greater in the controls, but smaller in the patients, than for central viewing. In the second experiment, a staircase procedure was used to find the contrast of a peripherally viewed grating of either 4 or 1.2 c/deg which apparently matched that of a centrally viewed grating of the same spatial frequency. Patients needed more contrast (about 1.6 times, at both spatial frequencies) than controls for a match. These results suggest that contrast gain may be lowered in the peripheral retina in Parkinson's disease, perhaps because of an abnormality of dopamine amacrine cells, whose density peaks in the peripheral retina.

INTRODUCTION

There is increasing evidence for visual abnormality in Parkinson's disease. It is well established that the latency of the visual evoked potential (VEP) is increased in the illness (Bodis-Wollner and Yahr, 1978; Gawel *et al.*, 1981). The retinal dopaminergic origin of this effect is suggested by the findings that the large inter-ocular differences found in some patients can be reduced by dopaminergic therapy (Bodis-Wollner *et al.*, 1982), and that the concomitant increase in pattern electroretinogram (PERG) *b*-wave latency can also be reduced by drug therapy (Pierelli *et al.*, 1988). Similarly, the latency of the pupillary light reflex is increased in Parkinson's disease, consistent with a retinal origin for the abnormality (Beaumont *et al.*, 1987). There are known to be dopaminergic amacrine neurons in the retina in many species, including man (Frederick *et al.*, 1982).

The anatomical site of psychophysically measured visual changes is often less easy to localize than those of, for example, the PERG. Bodis-Wollner *et al.* (1987) have reported losses of spatial and temporal contrast sensitivity, and Regan and Neima (1984) losses of sensitivity to low contrast letters, which could originate in the retina. However, Regan and Maxner (1987) have found orientation-specific losses of contrast sensitivity, which may involve the cortex, since orientation selectivity is first found there in the ascending visual system of the cat and the monkey (Hubel and Wiesel, 1962, 1968).

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Thus visual losses in Parkinson's disease may occur at several anatomical sdites, though the electrophysiological evidence suggests that they include the retina.

The density of dopamine amacrines in rhesus monkey parallels that of the rods (Mariani *et al.*, 1984). Thus they are sparse or absent in the fovea, and their density is highest some degrees into the periphery. In the parkinsonian retina, the normal concentric ring organization of dopamine neurons in the perifovea appears to be disrupted, and the density of fibres diminished (Nguyen-Legros and Savy, 1988). If these cells are indeed hypoactive in Parkinson's disease, as the VEP and some of the psychophysical evidence suggests, then one might expect peripheral vision in Parkinson's disease to be particularly affected. On the assumption that retinal dopamine hypoactivity is reflected in a loss of contrast sensitivity for medium spatial frequencies (Bodis-Wollner *et al.*, 1987), we tested parkinsonian patients on two tasks which are known to be affected in normal subjects by a variation in physical contrast. In the first experiment we measured the elevation in the contrast threshold for a grating, after adaptation to a high-contrast version of the grating, both in central and peripheral vision. Threshold elevation is known to vary with adapting contrast (Blakemore and Campbell, 1969; Georgeson and Harris, 1984). In the second experiment, we measured the amount of contrast needed for a peripherally viewed grating to match apparently the contrast of a simultaneously presented foveally viewed grating. If neurally signalled contrast is especially attenuated in the parkinsonian peripheral retina, there should be a reduction in threshold elevation for peripherally viewed gratings, and an increase in the contrast needed to match a peripheral to a foveal grating.

EXPERIMENT 1: CENTRAL VERSUS PERIPHERAL ADAPTATION

Methods

Apparatus

Vertical gratings with a sinusoidal luminance profile were generated on the face of a Tektronix 608 display oscilloscope with a green phosphor. The necessary waveforms were produced by a digital generator, whose principles are described by Harris *et al.* (1982), and which was programmed between frames by an Apple II microcomputer. The frame rate was 100 Hz, and the mean luminance held constant at 125 cd/m^2. In the range of contrasts used in the experiment, contrast [measured with a photopic photocell; *see* Harris *et al.* (1987)] varied linearly with the voltage applied to the Z amplifier of the oscilloscope. The oscilloscope screen subtended a retinal angle of 6 degrees wide × 3 degrees high, and was mounted in a dark surround. A small black fixation point was provided in the centre of the screen for central viewing. To achieve peripheral viewing, two other fixation points [small green light-emitting diodes (LEDs)] were mounted in the surround on an imaginary horizontal line running through the centre of the screen, one 4 degrees to the left of the left edge of the screen, the other 4 degrees to the right of the right edge. Two push buttons enabled the subject, whose head was stabilized with a chin-rest at a viewing distance of 114 cm, to increase or decrease the contrast of the grating on the screen. Simultaneous depression of both buttons signalled to the computer that a threshold had been set. Apart from a dim lamp which illuminated the computer keyboard and was shielded from the subject and display oscilloscope, the experimental room was dark.

Procedure

Measurements were made with two kinds of stimuli, stationary gratings or gratings oscillating through their spatial period at 8 Hz. At the start of the experiment, one of these was chosen at random, and all measurements made on that before those on the other were begun. For each type of grating, the order in which the different fixation conditions were allocated was also randomly chosen. For each fixation condition, the subject first spent 2 min adapting to the mean luminance of the screen, and then had 3 min practice in setting contrast thresholds, with the method of adjustment. Subjects were instructed to maintain fixation on the designated point throughout each condition. Visual inspection of the subjects' eyes suggested that this instruction was obeyed. Sensitivity was tested at seven spatial frequencies ranging from 0.1 to 16 cycles per degree (c/deg). On each presentation, a spatial frequency was randomly selected by the computer, until the subject had completed five trials at each spatial frequency. A tone sounded when each presentation (initially zero contrast) began, and again when the subject signalled to the computer that a threshold had been set. For the stationary gratings, subjects were asked to adjust the contrast of the grating until they could just detect some luminance modulation ('pattern threshold') and, for the oscillating gratings, until they could just detect flicker or motion ('movement threshold').

Once the contrast sensitivity function had been measured, a cyclical adapt/test procedure for measuring threshold elevations was begun. The adapting and test stimuli were always 2 c/deg gratings. The adapting contrast was always 1.4 log units above the previously measured threshold contrast at 2 c/deg. The duration of the first adapting period was 40 s, and that of the subsequent 'topping-up' periods was 5 s. At the end of each adapting period, a warning tone sounded to signal to the subjects that they should set a threshold as before. The computer timed the interval between the end of adaptation and the subject's signal that threshold had been set. Throughout the experiment, viewing was binocular, and natural pupils were used. In a comparison between the kind of patient group used here and normal controls, Beaumont *et al.* (1987) found no significant difference in pupil diameter at two luminances, one higher and one lower than the luminance of the present display.

The subjects were seven patients with a diagnosis of idiopathic Parkinson's disease made by a consultant neurologist, and seven age- and sex-matched normal controls, who were not taking any medication and had no history of neurological or psychiatric illness. The mean age of the patients was 60 yrs (SD = 8.6) and of the controls 58.6 yrs (SD = 6.7). All patients were receiving a mixture of L-dopa (100–800 mg/day) plus decarboxylase inhibitor, and in addition two were receiving bromocryptine, a dopamine receptor agonist. On the scale of Parkes (1982), the scores of the severity of their motor symptoms ranged from 5 to 19. The scale runs from 0 to 60, and patients with a score of 20 or less are considered to have mild symptoms. An eighth parkinsonian subject began the experiment, but could not cope with the adjustment task. All subjects gave informed consent to participate in this investigation.

Results

The contrast sensitivity functions for both groups and types of grating are shown in Fig. 1, from stimuli presented centrally and in the left visual field (data from the right visual field were very similar to those from the left). Although the mean data suggest a loss of sensitivity at medium spatial frequencies in all conditions for the patient group, the differences between patients and controls were not significantly different (by ANOVA) in any of the conditions. However, the trends for the centrally fixated gratings are similar to those reported by Bodis-Wollner (1988) for a similar patient population.

Inspection of the threshold elevations showed that there were no differences between the results for the two peripheral conditions for either subject group or type of grating, and so the data were combined to give a mean peripheral elevation. The threshold elevations (expressed as the logarithm of the ratio of post- and pre-adaptation thresholds) are shown in Fig. 2. Elevations were always larger for the stationary gratings in both groups, and, for central viewing, the patients showed slightly larger threshold elevations than the controls. In peripheral vision, elevations were greater in the controls for both stationary and moving gratings than for central viewing. For the patients, however, the opposite is true: the peripheral elevations are lower than for foveal viewing. This was confirmed by ANOVA: there was a significant interaction between locus of presentation and patient group (for stationary gratings F = 12.53, d.f. = 1,12; $P < 0.01$; for moving gratings, F = 16.19; d.f. = 1,12; $P < 0.01$).

As might be expected from the results of the ANOVA, the pattern of results from individual patients consistently followed the group trend. In only single cases (different patients for stationary and moving gratings) were peripheral threshold elevation higher than central elevation.

Post hoc Newman-Keuls comparisons were made between the mean threshold elevations, of which the results were as follows: patients versus controls, central, insignificant for both stationary and moving gratings ($P > 0.05$); patients versus controls, peripheral, significant for both moving ($P < 0.01$) and for stationary

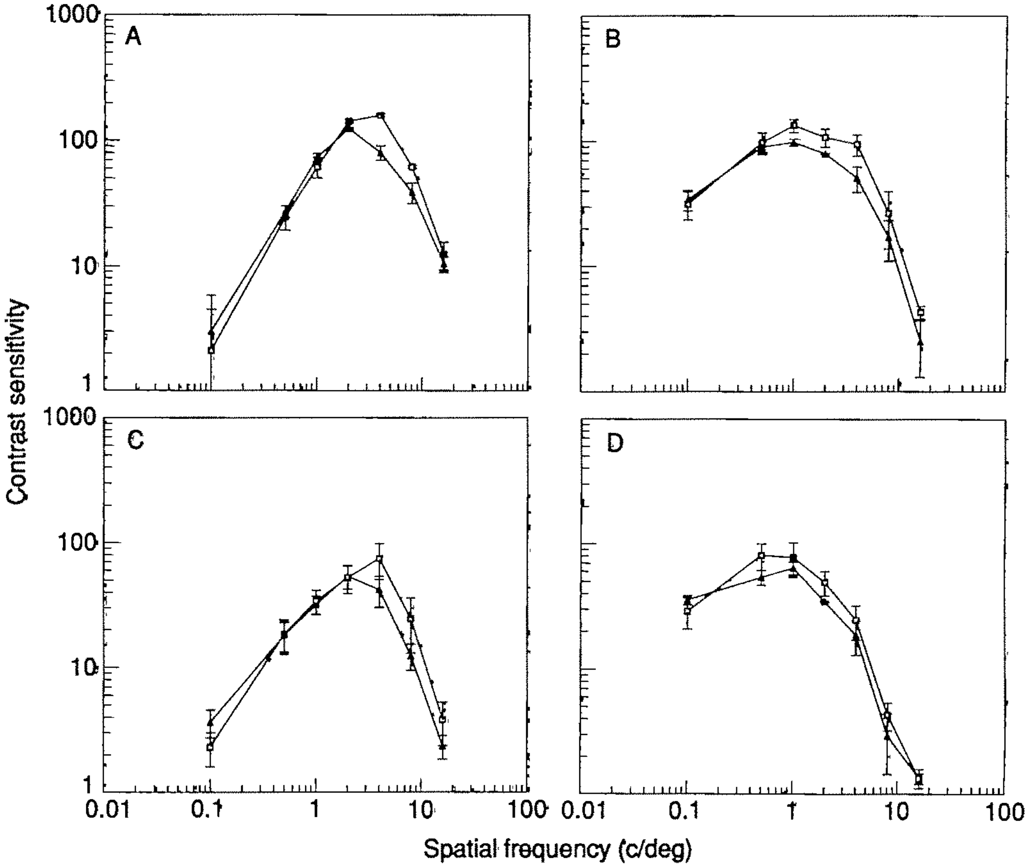

FIG 1. Contrast sensitivity functions for a group of seven parkinsonian patients (triangles) and a group of seven normal age-matched controls (squares). Data points are means of five settings by each of seven subjects. Sensitivity is the reciprocal of contrast at threshold. Vertical bars are standard errors. See text for more details. A, sensitivity for stationary, centrally fixated gratings. B, sensitivity for centrally fixated gratings oscillating sinusoidally through their spatial period at 8 Hz. C, sensitivity for stationary gratings in the left visual field. D, sensitivity for gratings in the left visual field oscillating sinusoidally through their spatial period at 8 Hz

gratings ($P < 0.05$); patients, peripheral versus central, insignificant for both stationary and moving gratings ($P > 0.05$); controls, peripheral versus central, significant for both moving ($P < 0.01$) and for stationary gratings ($P < 0.05$).

The mean times to set post-adaptation thresholds for moving gratings were: patients, central, 8.8 s; peripheral, 11.7 s, controls, central, 9.6 s; peripheral, 10.9 s. For stationary gratings the mean times were: patients, central, 7.8 s; peripheral, 10.3 s; controls, central, 10.1 s; peripheral, 11.5 s. None of these small differences between the groups was significant by ANOVA, and so do not support the possibility that the large differences of peripheral threshold elevation between the groups arose because the patients' motor difficulties in setting thresholds allowed more time for decay.

One can ask to what extent the severity of patient's symptoms correlated with size of threshold elevation. Spearman's Rank correlation coefficients were calculated between scores on the Parkes (1982) scale and the differences between central and peripheral threshold elevations, since the latter might reflect the relative impairment of peripheral vision. However, though positive, the correlations were weak and insignificant, both for stationary (+0.428) and moving (+0.05) gratings.

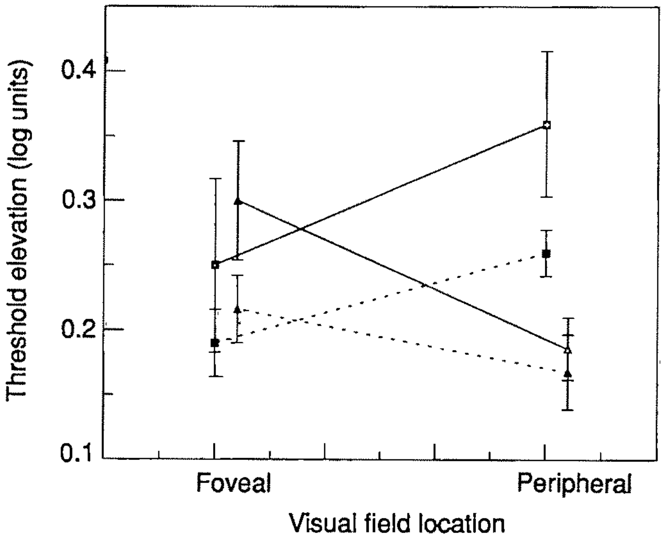

FIG. 2. Threshold elevations after adaptation to a grating whose contrast was 1 4 log units above its threshold contrast, for a group of parkinsonian subjects (triangles) and a group of normal age-matched controls (squares). Data points for foveal viewing are means of five measurements by each of seven subjects, those for peripheral viewing are means of 10 measurements (five in left visual field, five in right visual field) by each of seven subjects. Solid lines join data points for stationary gratings, broken lines for oscillating gratings Vertical bars are standard errors See text for more details

Discussion

Although the group differences between patients and controls were not statistically significant, the contrast sensitivity functions suggest losses of sensitivity above about 1 c/deg in the Parkinson's disease group. For lower spatial frequencies, sensitivity is, if anything, enhanced, as reported for centrally viewed stationary gratings by Bodis-Wollner (1988). The most dramatic difference between the groups is in the comparison between the central and peripheral threshold elevations. In the controls these are higher, and in the patients lower for peripheral than for central viewing.

Although the patients' threshold elevations were slightly higher in central vision, the differences from controls were not significant on the Newman-Keuls tests. These small differences may reflect the fact that the patients tended to set post-adaptation thresholds more quickly than the controls in central vision.

EXPERIMENT 2: CONTRAST MATCHING BETWEEN FOVEA AND PERIPHERY

Introduction

In normal individuals, threshold elevation can be reduced by reducing the contrast of the adapting grating. It is tempting, therefore, to suppose that some change in the parkinsonian peripheral visual system, such as a reduction in contrast gain, underlies this aspect of the data. If so, then a peripherally viewed grating should appear of lower contrast in Parkinson's disease than in normal subjects. Since threshold elevations for centrally viewed gratings were similar in patients and controls in Experiment 1, one way to test this hypothesis is to obtain contrast matches between contrally and peripherally viewed gratings. If the hypothesis is correct, Parkinson's disease patients should require peripheral gratings of higher contrast to obtain a match.

Methods

Apparatus

The apparatus was as in Experiment 1, with the following exceptions. (i) The oscilloscope screen was divided electronically into two about its vertical midline, so that two gratings, whose contrast was independently variable, could be presented side by side. (ii) The oscilloscope face was masked down to leave two circular apertures, each 2.5 degrees in diameter, with their centres horizontally separated by 9 degrees, in a dark surround. (iii) The viewing distance was held constant at 57 cm with a chin rest. (iv) Viewing was monocular, through the natural pupil.

Procedure

The subject, whose left eye was covered with an opaque patch, gazed at the right-hand aperture, so that the left aperture fell in his left visual field. On each trial, stationary gratings of the same spatial frequency were simultaneously presented for 500 ms in both apertures. Warning tones marked the onset and offset of each presentation. The contrast of the foveally viewed grating was always 20%. The subject held two push-buttons, one in each hand, and his task was to judge whether the left or right (peripheral or central) grating had the higher contrast, and to signal this judgement to the computer with the appropriate push-button. The next presentation was made 3 s after each response.

The point of subjective equality of the contrast of the gratings was measured with a staircase procedure. If the subject decided that the grating on the left had higher contrast, its contrast was reduced on the next presentation. If he decided that the grating on the right was of higher contrast, the contrast of the left grating was increased on the next presentation. The computer stored the contrast values at which the subject's decision changed from left to right or vice versa, until 10 reversal points had been measured. Two such staircases, randomly interleaved, were run, one starting with a contrast of the left-hand (peripheral) grating of 30%, the other with a contrast of 15%. The step size of each staircase was 0.12 log units. The point of subjective equality was taken to be the mean of the last six reversal points of each staircase.

The entire procedure was run twice, once for each of two spatial frequencies, 1.2 and 4 c/deg, and preceded by a 5 min session during which the subject adapted to the mean luminance and practised making the required judgements. The laboratory was dimly lit during the experiment: measured with a Salford Electrical Instruments (SEI) photometer, its white walls had a luminance of about 1 cd/m^2.

The subjects were 10 patients with a diagnosis of Parkinson's disease, made by consultant neurologist. Their mean age was 64.2 yrs (SD = 5.6). They were all stabilized on dopaminergic medication (L-dopa: 300–800 mg/day+decarboxylase inhibitor). In addition, six were taking anticholinergic drugs, and two bromocryptine. On the Parkes (1982) scale, their symptom scores ranged from 2 to 24. Ten control subjects, who had no history of neurological or psychiatric illness, and were not taking medication, were also tested. Their mean age was 64.2 yrs (SD = 7.9). All subjects gave informed consent to participate in this investigation.

Results

The data are plotted in Fig. 3. In both patients and controls, more contrast was required to match the higher spatial frequency. At both spatial frequencies, the patients required more peripheral contrast to obtain a match than the controls. The ANOVA confirmed the significance of these differences: for the difference between patients and controls, F = 21.8, d.f. = 1,18, $P < 0.01$; and for the difference between spatial frequencies, F = 20.5, d.f. = 1,18, $P < 0.01$. However, the interaction between groups and spatial frequency (greater difference between patients and controls at the higher spatial frequency) was not significant: F = 3.13, d.f. = 1,18, $P > 0.05$. Indeed, the factor by which the matched contrast of the peripheral grating in the patient group exceeded that of the control group was about 1.6 for both spatial frequencies.

Spearman's Rank correlation coefficients were calculated between the Parkes scores of severity and the matched contrasts of the peripheral grating. The correlations were positive, but small and insignificant (+0.07, for the 1.2 c/deg gratings; +0.17, for the 4 c/deg gratings). However, the correlation between the contrasts at both spatial frequencies was significant (+0.69; n = 10; $P < 0.05$). Thus a patient who needed a high contrast to match the 1.2 c/deg gratings also tended to need a high contrast to match the 4 c/deg gratings. However, there was only a very weak correlation between severity of motor symptoms, as estimated by the Parkes test, and losses in the peripheral visual field, as measured by contrast matching.

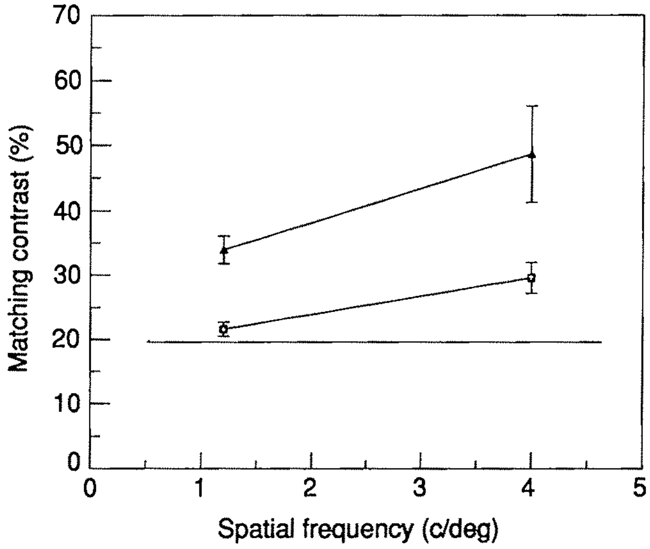

FIG 3. Contrasts, at apparent contrast match, of a grating lying 9 degrees from the fovea and compared with a foveally viewed grating of the same spatial frequency for a group of 10 parkinsonian subjects (triangles) and a group of 10 normal age-matched controls (squares). Matches were obtained with a two-alternative forced-choice staircase technique Data points are means of last six reversal points of two randomly interleaved staircases from each of 10 subjects Vertical bars are standard errors The horizontal line on the graph represents the contrast at physical match. See text for more details

Discussion

These results seem clear-cut: in only one case (at the higher spatial frequency) was the contrast at match for a patient less than for his age-matched control. They suggest that perceived contrast is reduced in the periphery in Parkinson's disease. They are of course also consistent with the possibility that foveal contrast is enhanced in Parkinson's disease. However, this idea is not supported by the evidence for reduced contrast sensitivity in the illness from other studies, or by the contrast thresholds measured in this study. The slightly (but not significantly) larger threshold elevations found for central viewing in the patients in Experiment 1, can be accounted for by the faster post-adaptation threshold settings by the patients, which would allow less time for adaptation to decay, and so give larger threshold elevations.

GENERAL DISCUSSION

Previous studies of the perception of luminance modulated gratings in Parkinson's disease have been concerned only with threshold measurements. Although we found a tendency towards abnormalities in contrast thresholds, which are of the same kind as those reported elsewhere for individual patients receiving dopaminergic therapy (Bodis-Wollner, 1988), the group differences between patients and controls were not significant. In contrast, in patients who were only mildly affected by the illness, our measurements involving processing of supra-threshold stimuli revealed larger and statistically significant abnormalities in peripheral vision.

Although this study has been guided by the idea that dopamine hypoactivity in the peripheral retina underlies the observed changes in parkinsonian vision, there are other possible abnormalities which should be considered. First, since natural pupils were used, a difference in pupil size between the groups might have produced differential effects on the foveally and eccentrically viewed gratings. However, Beaumont *et al.* (1987) found no significant differences in pupil diameter between a group of patients similar to (and including) those tested here and normal controls, so that this seems unlikely. Secondly, abnormalities of eye tremor might have differentially degraded perception of one of the gratings in the Parkinson's disease group. So, for example, in Experiment 2, in which subjects had to judge the apparent contrast of two simultaneously presented gratings, the peripheral grating, which would be activating larger receptive fields than the foveal grating, might have been more susceptible to increased retinal smearing produced by an increase in tremor amplitude or frequency in the Parkinson's disease group. Thus the apparent contrast of the peripheral grating might be reduced, and so more physical contrast would be needed to match it to the foveal grating. However, it should be noted that the abnormalities of threshold elevation found in Experiment 1 come from two threshold measurements, one before and one after adaptation. Any stimulus degradation would presumably affect both threshold measurements equally. The adapting contrasts (which were multiples of threshold contrast) were higher in subjects with higher pre-adaptation thresholds. Despite this, much smaller adapting effects were found in peripheral vision, but not in central vision, in the patient group. It is hard to explain this differential effect in terms of tremor-induced stimulus degradation, or in terms of other possible optical abnormalities in the patient group, such as clouding of the lens or media. Also, since efficiency of fixation was only crudely monitored by visual inspection of the subjects' eyes, differences between the groups in this might have contributed to the results. To take an extreme position, in Experiment 2, the controls might have tended to fixate between the gratings to a greater extent than the patients, thus bringing the gratings onto more similar retinal regions and so more nearly equalizing the contrast needed for a match. In Experiment 1, the same tendency would presumably have to be suggested for the eccentrically viewed stimuli, and might account for the enhanced contrast sensitivity in the control group. However, it is not clear how this would account for the pattern of threshold elevations, unless there were some pronounced non-monotonicity in the change of threshold elevation with eccentricity. Although several studies have reported abnormalities in parkinsonian eye movements, there does not seem to be evidence that patients have problems with fixation. Shibasaki *et al.* (1979), who found abnormalities of saccadic and pursuit eye movements, also report that, in a group of 19 Parkinson's disease patients comparable to those tested here, 'the EOG [electro-oculogram] at rest and that on forward gaze at the primary position were normal in all cases'. These considerations suggest that group differences in fixation behaviour do not offer a parsimonious explanation of the data.

Although an explanation based on difference of fixation or eye tremor cannot be conclusively ruled out, it appears plausible to try to acount for the results in terms of changes in the retina or beyond. Since the retina is known to encode contrast and to be abnormal in some parkinsonian patients, it may not be necessary to consider other visual sites. As noted in the Introduction, Mariani *et al.* (1984) and Nguyen-Legros and Savy (1988) found that dopamine amacrine cells are denser in the periphery than in the fovea in rhesus monkey and humans, respectively. If these cells are involved in the process of light adaptation, in which contrast gain (or the spatial properties) of visual channels are known to change (Shapley and Enroth-Cugell, 1984), their hypoactivity could underlie the present data.

The functional role of retinal dopamine amacrine cells is still uncertain. However, it is known that they release dopamine in response to retinal illumination (Iuvone *et al.*, 1978*a,b*), that they have large receptive fields (Ehinger, 1983), that topically applied dopamine can enhance the transient response of some cat ganglion cells (Thier and Alder, 1984), and alter the coupling via gap junctions of carp horizontal cells, perhaps changing the summation area of receptive fields (Teranishi *et al.*, 1984). Ehinger (1983) suggested that dopamine amacrines might be involved in the changes in receptive field properties which accompany light adaptation. Because dopamine amacrines release dopamine in a graded fashion as retinal illuminance is raised, Beaumont *et al.* (1987) proposed that, in Parkinson's disease, the retina would behave like the normal retina adapted to a lower mean luminance. Thus one would expect to find losses of sensitivity for medium to high spatial frequencies, as reported for selected patients by Bodis-Wollner (1988) and as suggested by Fig. 1. The present data support this evidence, and in addition suggest that neurally signalled contrast is reduced above, as well as at, threshold and emphasize the role of the retinal periphery in parkinsonian visual abnormalities. It is worth noting that although when group data are compared the threshold effects in Experiment 1 are not statistically significant, the effects involving contrasts well above threshold in peripheral vision are both larger and significant.

There are several possible reasons for the absence of a significant positive correlation between scores on the Parkes scale and the visual changes found in Parkinson's disease. For example, one might question the sensitivity of the Parkes test in discriminating the severity of symptoms of patients who were only mildly affected. Another possibility is that, in its early stages, at least, the illness (and dopaminergic medication) differentially affect retina and basal ganglia, so that visual and motor symptoms do not correlate well. We cannot decide between these and other possibilities from the present data. A larger study, with a greater range of symptom severity, would be necessary before confident conclusions could be reached. Only one patient took part in both Experiments 1 and 2, so that the correlation between the two measures of peripheral visual loss cannot be estimated from the present data.

This study has implications for the interpretation of other results in the literature. Villardita *et al.* (1983) have described visual neglect in Parkinson's disease. Although this may involve structures in the brain, such as the frontal lobes, it also seems possible that inefficient processing by the peripheral retina contributes to visual failures. Conversely, Cegalis *et al.* (1977), Cegalis and Tegtmeyer (1980), and Cegalis and Deptula (1981) have reported enhanced detection of, and distraction by, peripheral stimuli in schizophrenia. Although they attribute this to 'broadened attention', it also seems possible that hyperactive dopamine amacrines, presumably amplifying the contrast of peripherally viewed stimuli, could underlie these effects.

Although visual changes are usually not the reason that parkinsonian patients first consult a physician, questioning often elicits reports that their vision is deteriorating. One of our parkinsonian subjects spontaneously reported that he felt that he was developing 'tunnel vision'. This is just the change which our present data suggest. As in glaucoma, in which the underlying changes may be slow and insidious, the deterioration may be gradual and so escape the sufferer's notice. It would not be detected by, say, a Snellen test. Since peripheral vision is likely to be important in tasks such as driving, it may be worthwhile to test it in cases of Parkinson's disease.

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CONTROL OF SIMULTANEOUS MOVEMENTS DISTINGUISHES DEPRESSIVE MOTOR RETARDATION FROM PARKINSON'S DISEASE AND NEUROLEPTIC PARKINSONISM

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SUMMARY

Patients with depressive motor retardation, neuroleptic induced parkinsonism or Parkinson's disease were tested on movement tasks requiring control of simultaneous movements. This was in order to determine whether these three groups of patients, who all show slowing of movements, also share the distinctive impairment of simultaneous movement control that is observed in Parkinson's disease. Though all three patient groups showed equivalent slowing on the motor tasks that were studied, the patterns of impairment were different. Only the patients with parkinsonism, either neuroleptic induced or from Parkinson's disease, showed additional slowing of a rapid ballistic elbow flexion movement when it was performed simultaneously with a rapid squeeze of the ipsilateral hand. Only patients with parkinsonism showed a significant increase in dual task interference on a bimanual bead and tapper task, compared with controls. The bead and tapper interference in patients with depressive motor retardation was between that of controls and parkinsonism. Having a bimanual skill had a large effect on the subjects' dual task interference on this task. The measures of dual task interference for the two tasks did not correlate with one another; difficulty running simultaneous motor programs does therefore not explain the interference that is observed when tapping is performed while the other hand simultaneously performs a dextrous motor task. Only patients with parkinsonism showed increased fatigue on the tapping task. The patients with depressive motor retardation did have elevated scores on a clinical rating of parkinsonism. Nevertheless there are clearly defined differences between the movement disorder observed in patients with depression, and that observed in parkinsonism. The patterns of impairments in patients with neuroleptic parkinsonism were very similar to those of Parkinson's disease.

INTRODUCTION

Clinically there is much in common between the motor disturbance of depressive motor retardation and that of Parkinson's disease. Rogers *et al.* (1987) compared the motor disorder of Parkinson's disease with that of depression. An unselected group of patients with depressive illness had significantly elevated scores when rated on the Webster rating scale, a standard rating scale for parkinsonism. Patients with depressive motor retardation failed to score on tremor and rigidity, but scored on all other items of the Webster rating scale (Webster, 1968). Studies looking in detail at the voice characteristics of these two groups of patients confirm this clinical impression (Darby *et al.*, 1984). Mandell *et al.* (1962) were keen to emphasize the similarities: 'many features of depression including . . . slowness of movement are a reflection of the malfunction of the

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extrapyramidal motor system and are concomitants of the akinetic and rigid features of the parkinson syndrome'.

Is, therefore, depressive motor retardation simply a *forme fruste* of parkinsonism? One way of testing this possibility is to study patterns of movement control which are characteristically disturbed in parkinsonism, in patients with depressive motor retardation.

Control of simultaneous movements is impaired in parkinsonism (Schwab *et al.*, 1954). Benecke *et al.* (1986) found a very clear distinction on a test of simultaneous movement control between normals and patients with Parkinson's disease. The present study has looked at simultaneous movement control in depressive motor retardation.

In addition, the present study set out to answer a question set by Miller in the discussion of Chase's (1972) paper on drug-induced extra-pyramidal disorders; does neuroleptic-induced parkinsonism result in the impairment of simultaneous movement control that is to be observed in Parkinson's disease? Dopamine receptor blockade is the probable explanation for both the anti-psychotic effect of typical neuroleptics (Johnstone *et al.*, 1978), and neuroleptic-induced parkinsonism (Marsden and Jenner, 1980). The observation that is not possible to distinguish, on clinical examination, the parkinsonism of Parkinson's disease from that produced by neuroleptics (Hardie and Lees, 1988), is therefore compatible with the notion that the fundamental disturbance responsible for the clinical syndrome of parkinsonism is a reduction in dopaminergic activity in the extra-pyramidal system. If, however, control of simultaneous movements is found to be normal in neuroleptic-induced parkinsonism, then this will suggest that disruption of the extra-pyramidal dopaminergic system is not responsible for the impairments of simultaneous movement control that are to be found in Parkinson's disease.

PATIENTS AND METHODS

Four groups were studied; 22 controls, 10 patients with depressive motor retardation, 10 patients with neuroleptic parkinsonism and 15 patients with Parkinson's disease. The subjects were all between 18 yrs and 70 yrs of age and were, except for the Parkinson's disease group, who were significantly older, well matched for age.

The 22 controls were recruited from officers, trainee officers and the congregation of the Salvation Army. None were on psychotropic or neurotropic medication, apart from one subject who was on chlorpheniramine, and all were free of neurological and psychiatric illness.

The 10 patients with depressive motor retardation had either never been treated with neuroleptics, or were free of neuroleptic medication for at least 6 mths. All were free of neurological illness and fulfilled DSM-III-R criteria for major depression (American Psychiatric Association, 1987); two were bipolar, the rest unipolar. They were a random series of depressed patients recruited by regular telephone screening of 32 acute adult psychiatry wards in 14 psychiatric hospitals covering a total catchment of approximately 1.5 million people in south London over a period of about 1 yr. Patients who were reported by nursing staff as having significant clinical motor retardation were examined. Only patients in whom examination confirmed the presence of significant motor retardation, and in whom this retardation had been reported in the clinical notes, were included in the study. Seven patients were on tricyclic antidepressants alone; one patient was on clomipramine in combination with lithium and tryptophan; one patient was on a combination of lithium and phenelzine and carbamazepine; and one patient was on diazepam alone.

The neuroleptic parkinsonism group were selected as showing striking parkinsonism that had developed only while on neuroleptic medication. The diagnoses for this group were manic-depressive illness (three), schizophrenia (three), schizo-affective (three) and one with an acute psychosis. These patients were recruited in the course of recruiting patients with depressive motor retardation, as described above. Three patients were on neuroleptics alone; six on a combination of neuroleptic and anti-cholinergic; and one on neuroleptic plus anti-cholinergic plus antidepressant.

Statistics

The SPSS/PC package (Norušis, 1988) was used throughout; *t* tests (procedure *t* TEST) were used to analyse differences between means of two groups, analysis of variance (procedure ANOVA) was used to analyse group effects across all four groups and to look at covariance effects and linear correlation coefficients (procedure CORRELATION) to analyse correlations between variables. All significance values are two-tailed, except for the analysis of all correlation coefficients which were one-tailed.

RESULTS

There were no significant differences between the groups on the NART estimate of intelligence or the distribution of sex (Table 1), though there was an excess of females in the neuroleptic parkinsonism group, and an excess of males in the Parkinson's disease group.

The ratings of parkinsonism (KCH-PDRS) (Table 1) were equivalent in the two parkinsonian groups (neuroleptic parkinsonism and Parkinson's disease), whereas the scores on the KCH-PDRS for the control group and the depressive motor retardation group were significantly different from one another, and each had significantly lower scores than the two parkinsonism groups. The significance of these differences were all less than $P = 0.001$ except for the difference between means for the depressive motor retardation group and Parkinson's disease ($P < 0.025$) and the non-significant difference between the scores of the two parkinsonian groups.

The depressive motor retardation group had the highest ratings of depression on the Hamilton Rating Scale. The depression scores in the two parkinsonism groups were equal, and were significantly greater than controls (Table 1).

Across all subjects the depression score on the Hamilton Rating Scale was found to correlate best (one-tailed $P < 0.001$) with the items of the parkinsonism rating scale measuring facial immobility ($r = 0.58$) and bradykinesia ($r = 0.55$). The items tremor, writing impairment, impairment of rapid alternating movements and rigidity showed little or no correlation with the Hamilton Rating Scale depression scores.

This finding was corroborated by analysis of the scores on the items of the parkinsonism

TABLE 1. GROUP CHARACTERISTICS

	Controls *(n = 22)*	*Depressive motor retardation* *(n = 10)*	*Neuroleptic parkinsonism* *(n = 10)*	*Parkinson's disease* *(n = 15)*
Age (yrs)	49.5 (16.4)	49 6 (12)	41.8 (19 1)	62.1 (5 1)
Range (yrs)	21–70	31–66	20–70	51–68
Sex (M:F)	8:14	6:4	3 7	11:4
NART (IQ)	106 (9.5)	106 (13)	104 (12)	110 (9)
Range	86–124	86–120	86–121	97–125
KCH-PDRS	1.8 (2.1)	14.7 (5.4)	29.8 (4.7)	28.0 (13.7)
Range	0–7.5	7.5–21.5	24.5–40.5	1–59.5
Hamilton Rating Scale (depression)	1.6 (2)	25.7 (2.8)	6.8 (3 4)	6.4 (4.7)
Range	0–7	22–31	3–12	0–15

Results are expressed as the means (±SD) of the group characteristics except for the ranges and the sex ratio for each group.

rating scale (KCH-PDRS) in the patients with depressive motor retardation compared with controls. The patients with depressive motor retardation had significantly greater scores on facial immobility and bradykinesia (for both $P < 0.001$). For speech and posture all controls scored zero, and the mean depressive motor retardation score was more than three SEM's greater than zero, indicating a highly significant difference. All other parkinsonism items were not significantly increased in depressive motor retardation.

Bead and tapper

The three index groups all tapped significantly more slowly than controls in both the simultaneous and the independent condition (all with $P < 0.05$) (Table 2). Using ANOVA (Norušis, 1988; SPSS/PC, option 10 to analyse covariate effects first) with parkinsonism score (KCH-PDRS) as the covariate, there were no longer significant differences between controls and depressive motor retardation on the independent tapping rate; the slowing of the depressive motor retardation group on this measure was associated with their greater parkinsonian signs.

In all groups there was a significant drop in tapping rate in the simultaneous condition ($P < 0.001$ for all groups). The two parkinsonism groups (Parkinson's disease and neuroleptic parkinsonism) had the same percentage fall in tapping rate on the simultaneous task (Table 2) and for both groups this was significantly less than controls ($P < 0.05$). The percentage fall in tapping rate on the simultaneous task in the patients with depressive motor retardation was between that of controls and patients with parkinsonism.

Part of the variance in performance of this task was explained by the presence or absence of bimanual motor skills. Analysing the results, using ANOVA with group as the main effect, and presence or absence of bimanual motor skills as the covariate effect, subjects with bimanual motor skills were found to have significantly smaller percentage reduction in tapping rate in the simultaneous condition (d.f. = 1, F = 7, significance of F = 0.011). The significant group effects that were observed in Table 2 were still found when the results were analysed using ANOVA with bimanual motor skill as a covariate.

The regularity of the rhythm of tapping was studied by analysing the coefficient of

TABLE 2 PERFORMANCE ON A TAPPING TASK IN THE INDEPENDENT AND SIMULTANEOUS CONDITION

Group	*Independent*	*Simultaneous*	*Percent*
Controls (n = 20)	887 (133)	687 (174)	76.5 (11)
Depressive motor retardation (n = 8)	696* (174)	482* (187)	69 (19)
Neuroleptic parkinsonism (n = 7)	728* (204)	472* (203)	64* (17)
Parkinson's disease (n = 10)	693* (112)	445* (146)	64* (17)
Bimanual skill present (n = 17)	824 (179)	645 (203)	78 (14)
Bimanual skill absent (n = 28)	762 (165)	514** (189)	66** (15)

The results are the total number of taps [means (±SD)] in four 40 s trials of either the independent or simultaneous condition (*see* text). Percent is the number of taps in the simultaneous condition expressed as a percentage of the independent condition. $^*P < 0.05$ compared with controls; $^{**}P < 0.05$ compared with bimanual skill present.

variation of the intertap intervals. In the independent condition there was no significant difference in the variability of tapping rate of control subjects and patients with depressive motor retardation (Table 3). The variance of tapping rate of the two groups with parkinsonism were similar and significantly greater than both the controls and the depressive motor retardation group. In the simultaneous condition all patient groups had significantly greater variance of tapping rate than did controls, and did not differ significantly from one another (Table 3). The variance of the intertap interval in the simultaneous condition was highly correlated with the degree of dual task interference observed (tap percent) ($r = -0.73$, $P < 0.001$).

TABLE 3 THE VARIANCE OF THE INTERTAP INTERVALS

Group	*Independent*	*Simultaneous*
Controls (n = 20)	16.7 (9.0)	38.3 (21.1)
Depressive motor retardation (n = 8)	22.4** (10.0)	65.4* (41.0)
Neuroleptic parkinsonism (n = 7)	37.8* (15.9)	63.5* (12.9)
Parkinson's disease (n = 10)	38.9* (20.1)	67.3* (23.6)

The means (±SD) of the coefficients of variation of the intertap intervals for the four 40 s trials of tapping in the independent and simultaneous conditions. *$P < 0.05$ compared with control, **$P < 0.05$ compared with the combined parkinsonism groups.

Wells (1909) described in some detail the tapping rhythms he observed in patients with manic-depressive illness. He considered depression to be characterized by both a slow tapping rate, but also, somewhat surprisingly, a relative absence of the normal fatigue in tapping rate observed in controls when asked to tap as fast as possible for 30 s. On the other hand, fatigue on rapid alternative movements is characteristic of parkinsonism (Schwab *et al.*, 1959).

The tapping rates were therefore analysed to study the rates of fatigue during the course of each 40 s trial to see whether rates of fatigue would distinguish depressive motor retardation from parkinsonism.

Figure 1 shows the decline in tapping rate with time for the four groups. For all groups the fatigue of tapping rate tended to be slightly greater in the simultaneous condition (results not shown). The results shown in Fig. 1 are the average of the independent and simultaneous condition. In both the first and the last 10 s periods the tapping rates, expressed as a percentage of the overall tapping rate, of both the neuroleptic parkinsonism and the Parkinson's disease groups were significantly different ($P < 0.01$) from controls. There were no significant differences between the time course of the tapping fatigue of controls and patients with depressive motor retardation. These differences were confirmed by repeated measures ANOVA (Norušis, 1988) which demonstrated an highly significant group effect on the change in tapping rate across the four 10 s periods of each 40 s trial (F approximately 3.4, degrees of freedom for hypothesis = 9, $P = 0.002$).

Flex and squeeze

Typical plots of the flexion movements of one subject from each of the four groups are shown in Fig. 2. In the majority of subjects the fast upsweep was followed by a

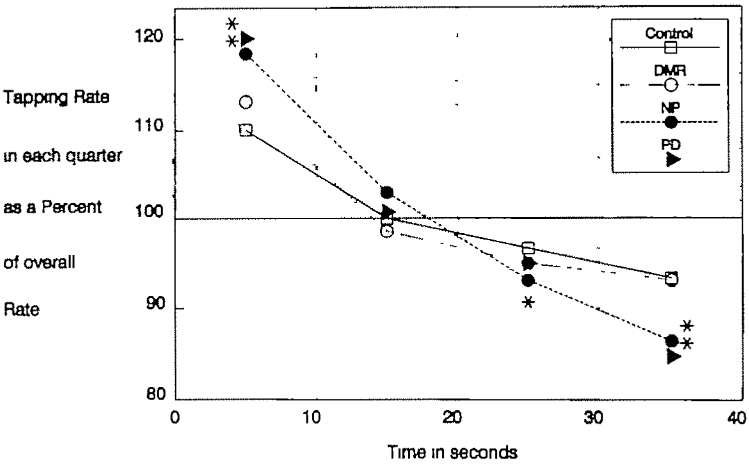

FIG. 1. The decline in tapping rate over time in the four groups, controls, depressive motor retardation (DMR), neuroleptic induced parkinsonism (NP), and Parkinson's disease (PD). The rates over the eight trials of 40 s for each subject have been averaged *$P < 0.01$ compared with controls.

slight overshoot of the movement past its final resting position. There was generally an inflexion in the movement trace about 100 ms after the peak of the overshoot, as the acceleration of the movement back towards the baseline is reversed in order to bring the movement to rest. Inspection of the averaged sweeps indicates that this inflexion was observed in all conditions, except for the simultaneous movement in the two parkinsonian patients.

In the patient with neuroleptic induced parkinsonism and the patient with Parkinson's disease there is a large upward-going displacement of the difference plot during the rapid flexion phase of the movement (Fig. 2). This indicates that the averaged independent movement accelerates more quickly, to a higher velocity than the averaged simultaneous movement; this can be seen on inspection of the averaged independent and simultaneous sweeps. In the control subject and the patient with depressive motor retardation the averaged independent and simultaneous sweeps are closely matched and the difference plot shows no large displacement from the line indicating equivalence of the averaged sweep positions.

The results displayed for the four subjects in Fig. 2 were fairly representative of the differences found by analysis of the means for the four groups. In all patient groups the movement times for both the MTI and MTS conditions were significantly longer than for control subjects, except for the independent movement time observed in patients with Parkinson's disease (Fig. 3). However, when ANOVA (Norušis, 1988; SPSS/PC, option 10 to analyse covariate effects first) with parkinsonism score (KCH-PDRS) as the covariate was used to analyse the results, there were no longer significant differences between controls and depressive motor retardation on the movement times (MTI and MTS); the slowing of the depressive motor retardation group on these two measures was associated with their greater parkinsonian signs. There were no significant differences between the mean movement times of the patient groups, except for patients with

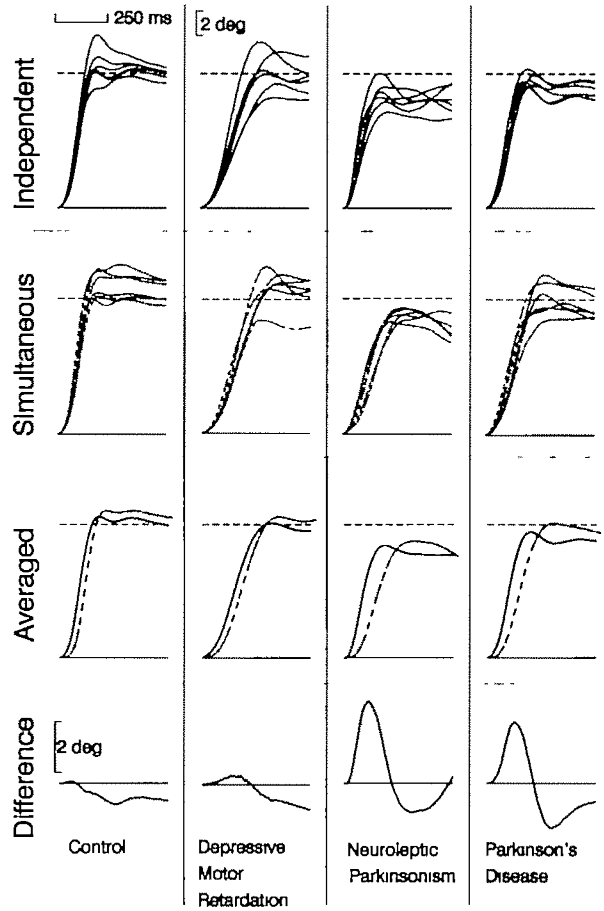

FIG. 2 The elbow flexion movement sweeps of typical subjects from each of the four groups are shown The sweeps have been displayed as the angular displacement over time from the start of the movement The start of the movement was identified manually, using the take-off point on the angular velocity plot (not shown), during the analysis of the movement time The subsequent 550 ms of movement was stored so that each sweep had zero milliseconds as the common origin indicating the start of the movement. In the three upper plots for each subject the single continuous horizontal line indicates zero angular displacement from the start of the movement, the dashed horizontal line indicates an angular displacement of 12° from the start of the movement. For each subject the six fastest independent (independent) and the six fastest simultaneous (simultaneous) sweeps are displayed in the top half of the figure. These sweeps have been averaged and displayed as the two averaged sweeps for each subject; the continuous line being for the averaged independent sweep and the dot/dash line the averaged simultaneous sweep In the averaged plots the start of the simultaneous average sweep has been displaced 25 ms to the right of the start of the independent sweep to allow both sweeps to be clearly visualized Therefore identical simultaneous and independent averaged sweeps will be displayed such that the upsweeps are parallel The difference plot is a plot of the difference in angular position, between the averaged independent and the averaged simultaneous sweeps for each subject, over time from the start of the movement. Displacement of the plot upwards, from the horizontal line indicating equivalence of angular position, indicates greater angular displacement of the independent sweep compared with the simultaneous sweep.

neuroleptic parkinsonism whose movement times, in both conditions, were significantly longer than patients with Parkinson's disease.

The MTI and MTS conditions were compared by subtracting the independent movement

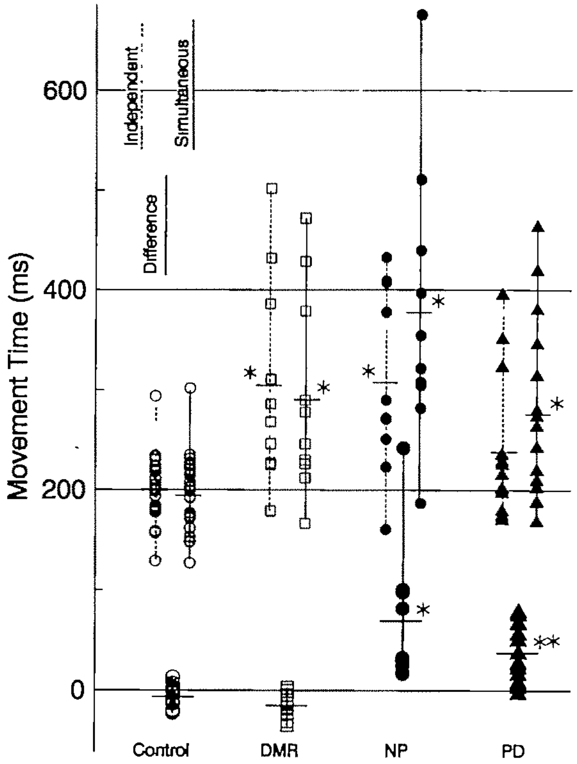

FIG. 3. The movement times in milliseconds of the elbow flexion movements, in the independent (the left-sided plot for each group) and simultaneous (the right-sided plot) condition, for the four groups. The Difference plots, near the horizontal axis, are the simultaneous movement time minus the independent movement time, for each subject. A positive value therefore indicates that the simultaneous movement time was longer. Open circles = controls; open squares = depressive motor retardation; closed circles = neuroleptic parkinsonism; closed triangles = Parkinson's disease. *$P < 0.02$, **$P < 0.001$ compared with controls.

time for each subject from their simultaneous movement time to give the difference time. There were significant differences (P values <0.01) between the difference time of the two groups of patients with parkinsonism compared with the difference time of both controls and patients with depressive motor retardation. A positive difference time means that the simultaneous movement is performed more slowly. The mean difference time was generally negative in the control subjects and patients with depressive motor retardation, but positive in the two patient groups with parkinsonism (Fig. 3). The best discrimination between parkinsonian patients versus non-parkinsonian patients was obtained using a cut-off of +6 ms for the difference time; all but two of the parkinsonian subjects ($n = 25$) had difference times greater than 6 ms, and all but two non-parkinsonian subjects ($n = 32$) had difference times less than 6 ms.

Therefore patients with depressive motor retardation, like control subjects but unlike patients with parkinsonism, do not show an additional slowing of elbow flexion when required to perform a simultaneous squeeze. These findings were confirmed by analysis of the peak velocities of the movements in the two conditions (Table 4).

TABLE 4 THE PEAK VELOCITIES OF THE FLEXION MOVEMENTS IN THE INDEPENDENT AND SIMULTANEOUS CONDITIONS

Group	*Independent*	*Simultaneous*	*Difference*
Controls (n = 22)	110 (20)	122 (20)	−11.1 (23.1)
Depressive motor retardation (n = 10)	81* (24)	82** (28)	−0.2 (6.6)
Neuroleptic parkinsonism (n = 10)	74** (29)	59** (22)	15.2* (10.3)
Parkinson's disease (n = 15)	100 (26)	84** (23)	15.2** (12.2)

The means (±SD) of the peak velocities (degrees/s) are shown for the independent and simultaneous condition. The difference is the independent peak velocity minus the simultaneous peak velocity; a positive score therefore indicates a slower simultaneous movement. *$P < 0.01$; **$P < 0.001$ compared with controls.

There were no significant differences between the mean amplitudes of the movements performed by the four groups, or the variance of the six fastest movement times, as assessed by the mean standard deviations of each individuals six fastest movement times for each condition, for the four groups (data not shown). The four groups had approximately the same performance on measurement of the amplitude of the squeeze movement of the simultaneous condition [control mean = 57% of individual's maximum squeeze (SD = 9%); depressive motor retardation: 48% (14%); neuroleptic parkinsonism: 45% (8%); Parkinson's disease: 51% (13%); control significantly different, $P < 0.05$, from depressive motor retardation and neuroleptic parkinsonism]. The four groups had approximately the same peak rate of increase of squeeze, expressed as percent maximum squeeze per second [control mean = 310 (SD = 58); depressive motor retardation 292 (17); neuroleptic parkinsonism 257 (61); Parkinson's disease 302 (22); neuroleptic parkinsonism significantly slower, $P < 0.05$, than control and Parkinson's disease].

Covariance of test results

Correlations, and analyses of covariance, between the four test results (dependent variables) and the patient characteristics (age, sex, NART IQ, Hamilton Rating Scale depression score and KCH-PDRS parkinsonism score) were performed. The four test results that were analysed were:

(i) The total tapping score in the four independent tapping trials (tap total); a measure of the tapping speed of the subject.

(ii) The percentage score in four simultaneous tapping trials compared with the total score in the four independent trials (tap percent); a measure of the impairment in tapping performance during simultaneous performance of another task.

(iii) The elbow flexion movement time in the independent condition (MTI).

(iv) The simultaneous minus the independent elbow flexion time (MTDIF); a measure of the slowing of elbow flexion movement in the simultaneous condition.

Analysis of variance was performed to look for significant covariance of the five independent variables as covariates, with the four test measures using group as the main effect (option 9 of the SPSS/PC ANOVA was used to allow all effects to be analysed simultaneously).

Consistent significant interactions, found in both correlation and covariate analysis, were:

(i) Older subjects tapped more slowly (tap total) ($r = -0.47$, $P < 0.001$; $F = 13.3$, d.f. = 1, significance of $F = 0.001$).

(ii) Lower NART IQ scores were associated with lower percentage scores on the simultaneous tapping task (tap percent) ($r = 0.46$, one-tailed $P < 0.05$; $F = 5.62$, d.f. = 1, significance of $F = 0.024$).

(iii) Parkinsonism scores (KCH-PDRS) correlated significantly with all test measures. The best correlation was parkinsonism versus the difference time for simultaneous minus independent elbow flexion movements (MTDIF) ($r = -0.67$, $P < 0.001$; $F = 93$, d.f. = 1, significance of $F < 0.001$).

(iv) Hamilton Rating Scale depression scores correlated significantly with elbow flexion movement times (MTI) ($r = 0.42$, $P < 0.01$; $F = 16$, d.f. = 1, significance of $F < 0.001$).

Analysis of control subjects only, found a significant correlation between age and elbow movement speed (MTI) ($r = -0.55$, one-tailed $P < 0.01$) with older subjects performing more slowly, and a correlation between the clinical score of rapid alternating movements and percentage score on simultaneous bead and tapper performance (tap percent) ($r = -0.54$, $P < 0.01$).

The five items of interest of the parkinsonism score (bradykinesia, posture, rigidity, tremor and rapid alternating movements) all showed highly significant ($r > 0.4$ or < -0.4, one-tailed $P < 0.005$) correlations with all four test measures, except for tremor, which only correlated significantly with the MTDIF. The two largest correlations were for rapid alternating movements against both tap percent ($r = -0.59$, one-tailed $P < 0.001$) and MTDIF ($r = -0.65$, one-tailed $P < 0.001$).

Is the mechanism of slowing of independent movements in parkinsonism different from that in subjects without parkinsonism; in particular is motor slowing in parkinsonism closely associated with impairment in production of simultaneous movements whereas in non-parkinsonian subjects they are unrelated? To test this hypothesis separate correlation analyses were performed in those subjects with parkinsonism (neuroleptic parkinsonism and Parkinson's disease) and in those subjects without (controls and depressive motor retardation). The correlations between the four measures of motor performance were analysed (Table 5). The predicted relationship was only observed on the flex and squeeze task (Table 5). On this task for parkinsonian subjects elbow movement time (MTI) correlated significantly with impairment of simultaneous performance on that task (MTDIF) whereas it did not for non-parkinsonian subjects. However, on the bead and tapper task tapping speed (tap total) correlated with percentage reduction on simultaneous tapping (tap percent) in the non-parkinsonian subjects only. There was a much stronger correlation of tapping speed (tap total) with motor speed of elbow flexion (MTI) in parkinsonian patients than in non-parkinsonian patients. There was no correlation between the two measures of dual task impairment, tap percent and MTDIF, in either parkinsonian or non-parkinsonian subjects.

Separate analysis of the parkinsonian and of the non-parkinsonian subjects indicated that the best correlation of clinical ratings of rapid alternating movements was with elbow flexion movement-time (MTI) in parkinsonian subjects ($r = 0.53$, $P < 0.01$), but with

TABLE 5 CORRELATION ANALYSES OF THE FOUR MEASURES OF MOTOR PERFORMANCE

	Tap total	*Tap percent*	*MTI*	*MTDIF*
Tap total	1.00	0.09 n = 17	−0.57* n = 17	0.02 n = 17
Tap percent	0.54* n = 27	1.00	−0.43 n = 17	0.16 n = 17
MTI	−0.35 n = 27	−0.21 n = 27	1.00	−0.52* n = 25
MTDIF	−0.21 n = 27	−0.07 n = 27	0.26 n = 32	1.00

Correlation analyses on patients with parkinsonism (top right), and on patients without parkinsonism (bottom left). Tap total is the tapping speed in the independent condition; tap percent is the percentage reduction in tapping in the simultaneous condition; MTI is the independent elbow flexion movement time, MTDIF is the difference between the independent and the simultaneous elbow movement times. Spearman's correlation coefficients are given. *One-tailed $P < 0.01$.

tapping speed (tap total) ($r = -0.66$, $P < 0.001$) and with percentage reduction of tapping (tap percent) ($r = -0.54$, $P < 0.01$) in subjects without parkinsonism. The only correlations for NART IQ scores were with tapping speed (tap total) ($r = 0.54$, $P < 0.01$) and with percentage reduction of tapping (tap percent) ($r = 0.48$, $P < 0.01$) in subjects without parkinsonism. However, NART IQ scores and ratings of rapid alternating movements correlated significantly with one another in non-parkinsonian subjects ($r = -0.54$, $P < 0.01$); this correlation was not found in those with parkinsonism.

Depression scores (Hamilton Rating Scale) did not correlate with any measure of motor performance in patients with parkinsonism, but correlated with elbow movement speed (MTI) ($r = 0.60$, $P < 0.001$), tapping speed (tap total) ($r = -0.53$, $P < 0.01$), and with percentage reduction in tapping rate (tap percent) ($r = -0.44$, $P = 0.01$) in subjects without parkinsonism.

To determine whether age differences between the groups partly explained some of the group differences on the four dependent variables (tap total, tap percent, MTI and MTDIF), ANOVA was performed using age as the covariate effect and group as the main effect, and option 10 of SPSS/PC in order that any variance associated with age was examined first. All the group effects described remained, except for those on tap percent, the percentage reduction in tapping rate. For this dependent variable the difference between controls and Parkinson's disease now just failed to reach significance ($P = 0.057$). However, the difference between controls and the combined parkinsonism group remained significant ($P = 0.012$).

DISCUSSION

The patients with depressive motor retardation had elevated scores on a standard rating scale for parkinsonism. This finding is consistent with that of Rogers *et al.* (1987). The scores of the present population of depressed patients have been compared with those studied by Rogers *et al.* (1987). The mean score on the Webster (1968) parkinsonism rating scale of the 30 patients consecutively referred with depression in that study was five. Converting the parkinsonism scores of the depressives in the present study to Webster scores gives a mean score of 9 (SD = 2). This conversion is retrospective, and must therefore be regarded as an approximation, but does suggest that the population recruited in this study showed significantly more motor retardation than a 'control' series of depressives. In both studies elevated scores on facial immobility and reduced arm-swing (contributing to the rating 'bradykinesia' on the KCH-PDRS) were particularly associated with depression. On the other hand, tremor, rigidity and probably writing impairment ('writing' on the KCH-PDRS and contributing to 'bradykinesia of hands, including handwriting' on the Webster scale) were selectively elevated in the parkinsonism groups compared with depression.

In the present study both groups of patients with parkinsonism had elevated scores on a rating of depression. However, the slowing of patients with parkinsonism on the two tests did not correlate with depression scores. Depression scores correlated with motor speed only in non-parkinsonian subjects. It is unlikely that anti-depressant medication explained the motor retardation of the depressive motor retardation group. Glass *et al.* (1981) found no evidence of motor slowing in outpatient depressives on imipramine.

Motor speed

Slowing of simple motor tasks, either the initiation of movement as measured by simple reaction times (Martin and Rees, 1966; Weckowicz *et al.*, 1972) or the rate of motor task performance (e.g. writing: Nelson, 1953; Payne and Hewlett, 1960), may be observed in depression (*see* Miller, 1975, for review), but is not consistently found (Friedman, 1964; Gill, 1972). Bradykinesia, a slowness in initiating and carrying out motor acts, is a fundamental symptom of Parkinson's disease (Marsden, 1982). Reaction times and movement times are slow (Brumlik and Boshes, 1966; Evarts *et al.*, 1981).

Patients with depressive motor retardation and patients with parkinsonism demonstrated equivalent slowing of single rapid ballistic movements (independent elbow flexion movement time, Fig. 3). Previous studies have shown a greater increase in ballistic movement time, compared with controls, in Parkinson's disease (75%; Benecke *et al.*, 1986) than in depression (36%; Cornell *et al.*, 1984). However, in the present study the patients with depression had been selected for evidence of retardation, while the patients with Parkinson's disease had mild to moderate symptoms and the majority were on L-dopa.

Slowing of independent tapping was observed in all the patient groups and confirms previous findings both in depression (Wells, 1909; Weckowicz *et al.*, 1978) and Parkinson's disease (Talland and Schwab, 1964; Horne, 1973). In the present study it was associated with depression and with dual task interference on bead and tapper (in non-parkinsonian subjects), with speed of ballistic movements (in parkinsonian subjects) and with age. On the other hand, slowing of ballistic movements (independent elbow flexion movement time) was associated with age (in controls), with depression (in non-parkinsonian subjects) and with dual task interference on flex and squeeze (in parkinsonian subjects).

In the tapping task the depressive patients did not show ready fatigue, unlike those with parkinsonism. Wells (1909) also found that depressives tend to show little fatigue of tapping. Parkinsonians, on the other hand, show exaggerated fatigue of a task requiring repeated alternating movements (Schwab *et al.*, 1959). In the present study, scores on the clinical assessment of rapid alternative movement, which rely heavily on evidence of fatigue, distinguished depresson (little impairment) from parkinsonism (marked impairment). These findings therefore appear to be inconsistent with the observation that fatigue is a prominent complaint of depressed patients, and that their performance on some tasks does indeed show evidence of fatigue (Nelson, 1953; Friedman, 1964; Martin and Rees, 1966; Cohen *et al.*, 1982). It therefore seems likely that whether or not fatigue is found to be a prominent symptom of depressed patients will depend very much on the question or task that is asked of them.

Dual task performance

It has been suggested that dual task interference is best analysed by studying the rates of information transfer that are involved for each task, and the consequent competing demands they make on attentional resources (Bahrick and Shelly, 1958; Kantowitz and Knight, 1978). However, the information load of a simple key tapping task is negligible, yet the task is vulnerable to considerable interference by a second task that requires dextrous motor performance. Any complete account of dual task performance therefore has to be based on a model of attentional control which allows task interference to occur both at a central executive with limited capacity resources and at peripheral structures performing specific perceptual and motor tasks (Kahneman, 1973; Baddeley, 1986).

Information theories of dual task interference also fail to account for the effects of temporal compatibility on bimanual task performance (Peters, 1977; Klapp, 1979); conflicting rhythms in the two tasks results in a dramatic increase in interference. The tendency of normal subjects to organize bimanual motor tasks according to a single time-generator, or metronome, is preserved in Parkinson's disease (Cohen, 1970; Stelmach and Worringham, 1988; Horstink *et al.*, 1990).

Flex and squeeze. Analysis of motor control has tended to distinguish between single, target-directed movements, and complex motor patterns (Keele, 1981). The distinction is to a certain extent arbitrary because even single movements coordinate several muscles, but Marsden (1982) has used it with advantage to distinguish between motor programs and motor plans. Motor plans determine the selection and temporal coordination of a sequence of motor programs. They coordinate the switching of one motor program to another, and the running of simultaneous motor programs.

The interference shown by parkinsonian patients on the flex and squeeze task is probably a result of the difficulty they have running two motor programs at the same time (Benecke *et al.*, 1986). In the present study for some parkinsonian patients the shape of the elbow movement sweep was different in the simultaneous condition (Fig. 2), with loss of the inflexion just after the peak amplitude of the sweep has been reached. This presumably is because the normal triple burst electromyography pattern (agonist-antagonist-agonist) of the movement is lost (Benecke, 1989, pp. 67–68).

Most normal subjects showed a slight facilitation of elbow flexion speed when required to simultaneously squeeze with the hand (present study; Benecke *et al.*, 1986). Presumably the temporal matching of the two motor tasks allows muscle synergisms (Keele, 1981). Synergism between movements may develop during the learning of a motor skill (Kahneman, 1973, p. 158). Neither the present study nor that of Benecke *et al.* (1986)

have looked at learning effects on the simultaneous performance of flex and squeeze. This may be important because Parkinson's disease may impair learning of manual skills (Frith *et al.*, 1986).

Bead and tapper. In motor tasks which require aiming movements, the demands for attentional resources are particularly large at the beginning of the movement (Kantowitz and Knight, 1978; McLeod, 1980). In the present study tapping rate tended to slow down as the bead was being picked up and just before the start of the aimed movement to the other bowl, and this produced variance of the intertap interval. The variance of the intertap interval in the simultaneous condition was a good measure of the degree to which tapping performance was impaired by bead transfer. The largest variance was observed in patients with Parkinson's disease, and this may partly be a result of 'time-sharing'. Schwab *et al.* (1954) used this term to describe the tendency of their parkinsonian patients to stop one task (squeezing a pneumatic bulb with one hand) while performing another (drawing a triangle with the other, dominant, hand) and vice versa. However, in a slightly easier version of the task, Horstink *et al.* (1990) found that parkinsonians, while they were drawing a triangle with their other hand, were able to maintain the repetitive squeezing of the bulb at a reasonably constant rate; but the amplitude of the squeezes was smaller compared with their performance when they only had to squeeze the bulb. They therefore suggested that patients with Parkinson's disease do not have a disorder of time-sharing, but fail to shift attention to the task that is less externally cued.

However, 'time-sharing' and failing to 'shift attention' may in fact both be a result of the same fundamental handicap in Parkinson's disease. It seems likely that complex motor actions are enacted by running a sequence of motor programs and checking at intervals that the objectives are successful (Miller *et al.*, 1960; Marsden, 1982, fig. 10); for example, when a skilled pianist plays the piano the checkpoints at which behaviour is monitored and controlled do not occur after every stroke. It is then possible that switching attention, 'time-sharing' of *attention*, between two tasks occurs and yet both tasks continue uninterrupted; as a computer may attend to two printers such that each prints continuously. The impaired ability of parkinsonian subjects to make accurate predictive movements (Flowers, 1978) will increase the frequency with which they have to check the successful running of motor programs. The consequent drain on attentional resources will reduce the resources available for a subsidiary task. If the first task is difficult then there may be insufficient resources remaining to perform the subsidiary task; the subject will therefore demonstrate time-sharing of *performance*. But if the first task is relatively easy then sufficient resources may remain to allow continuous performance of the second task; but the reduced resources available may be manifest as a reduction in amplitude of this second task.

In the present study, slowing on the simultaneous bead and tapper task, as measured by the percentage reduction in tapping rate (tap percent), was observed in all subjects. The depressive motor retardation group fell midway between controls and the two parkinsonism groups on this measure of dual task interference. The only significant differences were found between controls and the two parkinsonism groups. Nevertheless depression scores in non-parkinsonian subjects did covary significantly with tap percent.

The simultaneous tapping rate, expressed as a percentage of independent tapping rate, for all studies that have used the bead and tapper task have been compared (Talland, 1962; Talland and Schwab, 1964; Gill, 1972; Horne, 1973; Taylor *et al.*,1986). In all studies, including the present study, the apparatus has been very similar. For control populations (n = 8) the mean percentage rate has varied between 61% and 85%, with a mean of 71%, with younger control groups tending to have a higher mean percentage. Parkinson's disease groups (n = 4) have had mean percentage rates of 40–64%, with a mean of 54%. The two depressed populations, Gill (1972) and the present study, have had mean percentage rates of 62% and 67%, respectively; in the Gill (1972) study the rate of 62% was significantly less than controls. The conclusion from this review mimics that of the present study; the measure is poor at discriminating between controls and patients with depression, and between patients with depression and those with parkinsonism.

Subjects who had a bimanual skill, either typing or playing a musical instrument, showed much less interference on the bead and tapper task. The percentage reduction in tapping rate in the simultaneous condition was almost as large in the non-skilled subjects as a group as it was in the parkinsonism patients as a group (Table 2). This may partly explain Talland and Schwab's (1964) observation that there is considerable overlap between control subjects and patients with Parkinson's disease on this measure. Dual task interference on this task also correlated with NART IQ, even after taking account of the effect of bimanual skill using analysis of covariance (results not shown). Previous studies have demonstrated an effect of age on bead and tapper performance (Talland, 1962) but this was not found in the present study.

Comparison between the tests

Two separate conclusions may be drawn from analysis of the correlations between the four measures of motor performance (Table 5). First, the motor abilities which the two tests are measuring are different from each other. Secondly, that the motor performance of parkinsonian subjects tended to correlate with variables which were different from those for subjects without parkinsonism.

Of the two tests used, the study of ballistic elbow flexion movements had the greater discriminatory power. Dual task interference on the bead and tapper task was observed in all subjects, and the large variance in performance within all groups hindered the identification of group differences. On the other hand, dual task interference on the flex and squeeze task was observed almost exclusively in subjects with parkinsonism; subjects without parkinsonism tended to show facilitation on dual task performance on flex and squeeze.

The difference time, a measure of dual task interference on flex and squeeze, was highly correlated with the total parkinsonism score (KCH-PDRS), and the items bradykinesia, tremor and rapid alternating movements, and with no other variables. On the other hand, the percentage reduction in tapping rate in the simultaneous condition only correlated moderately with the total parkinsonism score, and only with one parkinsonian item rapid alternating movements, but in addition, in non-parkinsonian subjects only, correlated with NART IQ, depression scores and the rate of independent tapping. Dual task interference on bead and tapper did not correlate with that of flex and squeeze. The ability to run two motor programs simultaneously therefore does not explain the dual task interference on the bead and tapper task.

What then are the psychomotor handicaps that contribute to impaired dual task bead and tapper performance in patients with parkinsonism? Parkinsonian subjects may have difficulty delegating the motor actions of the task to slave motor systems because they 'cannot trust to accurate predictive action' (Marsden, 1982). This will make greater demands on central resources. Greater structural interference might occur in motor systems responsible for organizing motor responses (Klapp, 1979; Gopher *et al.*, 1982), particularly in patients with Parkinson's disease with impaired sequencing/switching of motor programs (Angel *et al.*, 1970; Berardelli *et al.*, 1986; Benecke *et al.*, 1987). Switching set or switching attention might be subject to greater capacity interference at a central executive with reduced resources in Parkinson's disease (Brown and Marsden, 1988). Parkinson's disease may result in impairment of frontal lobe performance (Taylor *et al.*, 1986), known to be important in the control and coordination of bimanual movements (Leonard *et al.*, 1988).

The present study failed to demonstrate significantly greater dual task interference on the bead and tapper task in the depressed subjects than controls. Nevertheless, taken overall (*see* bead and tapper discussion above), the results do suggest a relationship between depression and poor dual task performance on this task.

If dual task performance in depression is impaired by a motivational deficit (Cohen *et al.*, 1982) or reduced effortful processing (Roy-Byrne *et al.*, 1986), while in parkinsonism it is a result of a more specific motor handicap, then two predictions may be made. First, dual task interference in depression will be particularly vulnerable to a subsidiary task that involves mental, as opposed to motor, effort. This could be tested by a series of experiments using subsidiary tasks with different demands on the cognitive and motor components of psychomotor processing (McLeod, 1978; Posner and Cohen, 1980). Secondly, because interference between two easy tasks is generally less vulnerable to reduced exertion of effort than is the interference between two difficult tasks (Kahneman, 1973), there should be a differential effect of task difficulty. The reduction in dual task interference on going from two difficult tasks to two easy tasks should be greater in depressed patients. Indeed it has been found that motor performance in depression speeds up when a second, but easy, cognitive task is simultaneously performed (Foulds, 1952; Shapiro *et al.*, 1962; Blackburn, 1975).

In conclusion, the present study has shown that it is possible to clearly distinguish the motor performance of patients with depressive motor retardation from those with parkinsonism. Equivalent slowing of movement in patients with depressive motor retardation is not accompanied by the particular patterns of impairment found in parkinsonism; dual task interference on the flex and squeeze task and fatigue on a tapping task. The flex and squeeze task will be a valuable tool to identify, with a specificity of greater than 90%, parkinsonism in patients on neuroleptic medication.

It seems likely that impairments of motivation and will are primarily involved in the motor retardation that may be observed in depressive illness. However, such processes are difficult to define and study directly (Kimble and Perlmutter, 1970) and, as was demonstrated in the present study, it is easier to define which processes do not cause depressive motor retardation. On the other hand, it seems likely that the akinesia of Parkinson's disease is a disorder of motor organization, and not of will, and that voluntary impulses encounter obstacles on their path to action (de Ajuriaguerra, 1975). Dopamine pathways in the basal ganglia are probably the neural substrate for the activating influence of motivation and willed intentions (Robbins and Sahakian, 1983; Frith, 1987). Nevertheless depression and parkinsonism have much in common (Rogers *et al.*, 1987). It has been shown that L-dopa improves memory performance in depressed subjects (Murphy *et al.*, 1972). Starkstein *et al.* (1990) found that cognitive impairment in Parkinson's disease is associated with depression, and that there is a specific interaction suggesting that similar processes may be impaired by both conditions. In the present study scores on a rating of parkinsonism were associated with the degree of motor slowing in patients with depressive motor retardation. Study of dual task processing in depression and in parkinsonism may further the definition of those processes that are unique to each condition, and those that are common.

Neuroleptic parkinsonism

The proportions of the patients with neuroleptic parkinsonism with each of the major diagnostic categories of functional psychoses (30% schizophrenia, 30% schizo-affective, 30% affective) are very similar to those in the series of Hardie and Lees (1988) (35%, 27%, 27%, respectively).

Parkinsonism due to neuroleptic medication was observed to produce the same impairments in the performance of simultaneous motor acts as does Parkinson's disease, and the degree and pattern of impairments on two different motor tasks were very similar in the two groups. This result supports the notion that the extrapyramidal dopaminergic system is involved in the selection and running of motor programs (Marsden, 1982).

In idiopathic Parkinson's disease the focus of dopamine loss is in caudate-putamen, rather than frontal cortex (Agid *et al.*, 1989). Neuroleptics, on the other hand, would be expected to show no preferential blockade of dopamine receptors in basal ganglia. Impairment of functions that depend on dopamine systems that lie outside of the nigrostriatal system should therefore be more evident in neuroleptic parkinsonism than in idiopathic parkinsonism, given equivalent degrees of parkinsonism. If dual task bead and tapper performance makes demands on both mental and motor processing, and if mental processing may be impaired by reduced dopaminergic activity in mesocortico-limbic pathways (Rogers *et al.*, 1987), then bead and tapper dual task interference should be preferentially impaired in neuroleptic parkinsonism. This was not observed, possibly because the neuroleptic parkinsonism group were younger; age has been shown to impair performance on this task (*see above*).

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SEQUENTIAL ARM MOVEMENTS IN PATIENTS WITH PARKINSON'S DISEASE, HUNTINGTON'S DISEASE AND DYSTONIA

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SUMMARY

We studied the performance of sequential arm movements in 14 patients with Parkinson's disease, nine patients with Huntington's disease and seven patients with arm dystonia. The results were compared with those from normal subjects. Subjects had to perform each movement of the sequence as fast as possible, stopping as briefly as possible between two successive movements. In one set of experiments, patients with Parkinson's disease drew four different geometrical patterns in a counter-clockwise direction. The patterns consisted of two, three, four and five segments of identical length. In a second set, the subjects drew a pentagon in a counter-clockwise and a clockwise direction and each side of the pentagon singly in a counter-clockwise direction.

All three groups of patients were slow in executing movements and in switching from one movement to the next. Only patients with Parkinson's disease took longer to perform the segments at the end of a sequence. In other words, their movement times lengthened progressively as the sequence progressed. This phenomenon could still be recognized when the direction and position of the segments were changed (pentagon drawn in the counter-clockwise and the clockwise direction) and when the extra-time needed, mainly due to the sequential nature of the task, was considered by computing the differences between movement times obtained during drawing of the pentagon and those obtained when each segment was traced singly.

This study demonstrates that sequential movements are abnormal in Parkinson's disease, Huntington's disease and dystonia and that in the performance of long motor sequences, the deficit in sequencing movements is exacerbated only in patients with Parkinson's disease.

INTRODUCTION

Patients with Parkinson's disease (Wilson, 1925; Draper and Johns, 1964; Flowers, 1975, 1976; Hallett *et al.*, 1977; Hallett and Khoshbin, 1980; Berardelli *et al.*, 1986*b*), Huntington's disease (Thompson *et al.*, 1988) and dystonia (Van der Kamp *et al.*, 1989) are slow in executing limb movements. They are also slow in performing more complex motor tasks (Schwab *et al.*, 1954; Benecke *et al.*, 1986, 1987; Berardelli *et al.*, 1986*a*). In Parkinson's disease, movement time measurements have shown that motor acts are executed more slowly when performed sequentially (Benecke *et al.*, 1987) than when performed singly. Similar abnormalities have been noted in patients with Huntington's disease (Thompson *et al.*, 1988), but no information has been published regarding patients with dystonia.

Movement time measurements during the performance of sequential motor tasks have

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so far been limited to sequences comprising only two movements. Interestingly, in Parkinson's disease, clinical observations have suggested that the degree of impairment of these complex movements depends largely on the number of motor acts within a sequence (Marsden, 1989). In other words, as the execution of a sequence progresses, the motor abnormalities become more and more evident.

To study this issue, we tested the ability of patients with Parkinson's disease in executing motor sequences comprising an increasing number of movements, and compared the results with those obtained in patients with Huntington's disease and dystonia affecting the upper limbs.

PATIENTS AND METHODS

Subjects

The study groups consisted of 14 patients with Parkinson's disease, 12 males and two females, aged 49–78 yrs (mean ± 1 SE, 62.9 ± 2.2 yrs); nine patients with Huntington's disease, all showing choreic movements, seven males, two females, aged 38–67 yrs (53 ± 4.1 yrs); seven patients with dystonia involving the upper limbs, five males, two females, aged 23–57 yrs (32.3 ± 4.5 yrs), and two groups of normal subjects of different ages: (i) five subjects, three males and two females, aged 24–40 yrs (31.6 ± 2.8 yrs); (ii) eight subjects, six male and two females, aged 44–74 yrs (58.7 ± 3.1 yrs). The younger group of normal subjects was used as control for the dystonic patients and the older group as control for the parkinsonian and choreic patients. All the normal subjects were relatives of the patients. Informed consent was obtained from all participants and the study was approved by the local ethical committee. Table 1 shows the clinical features of the Parkinson's disease patients, as assessed with the Unified Parkinson's disease rating scale (UPDRS); Table 2 shows those of the patients with Huntington's disease, as assessed by Marsden and Quinn's Chorea severity evaluation scale; Table 3 those of dystonic patients (for the rating scales, *see* Weiner and Lang, 1989). All the patients with Parkinson's disease were studied at least 6 h after the last drug administration and their clinical conditions were stable throughout the study. Patients with Huntington's disease and dystonia were studied while they were on their usual daily therapy regimen.

TABLE 1 CLINICAL FEATURES OF PATIENTS WITH PARKINSON'S DISEASE

Patients	*Age (yrs)*	*Sex*	*UPDRS**	*H and Y*
A.F.	59	M	8	2.0
D S	50	M	16	2.0
F.G.	69	M	33	4 0
D.A.	71	M	23	2.5
T.V.	61	F	18	2.0
B.L	56	F	26	3.0
C.G.	78	M	15	2.5
A.D.	66	M	24	2 5
V.M.	69	M	24	3 0
F.U.	49	M	25	3.0
M.L.	60	M	17	2.5
L.F	61	M	12	2 0
M A.	69	M	30	3.0
L.L.	63	M	35	4.0

*UPDRS = unified Parkinson's disease rating scale, the score refers only to the 'motor examination' section. H and Y = modified version Hoehn and Yahr staging (*see* Weiner and Lang, 1989).

TABLE 2 CLINICAL FEATURES OF PATIENTS WITH HUNTINGTON'S DISEASE

Patients	*Age (yrs)*	*Sex*	*Therapy*	*Total score*	*Huntington's disease Chorea score*
A.E.	49	M	–	27	17
T B	38	M	–	19	14
D M.	63	F	–	22	10
T.A.	64	F	Tiapride	31	19
P M.	47	M	Haloperidol	22	14
M.M.	34	M	–	22	18
F.E.	49	M	Tiapride	21	12
L.G.	67	M	Pimozide	32	21
M.R	66	M	–	26	14

Total and chorea scores using the Marsden and Quinn chorea evaluation scale (*see* Weiner and Lang, 1989).

TABLE 3 CLINICAL FEATURES OF PATIENTS WITH DYSTONIA

Patients	*Age (yrs)*	*Sex*	*Therapy*	*Type*	*Severity*
T.R	23	F	–	Brachial	Moderate
C.A.	25	F	Benzhexol	Generalized	Moderate
K G.	57	M	Benzhexol	Generalized	Mild
V.M	37	M	Benzhexol	Brachial	Mild
P A.	30	M	–	Brachial	Mild
S.G.	25	F	–	Brachial	Slight
T.C	29	M	Benzhexol	Generalized	Slight

The type and severity of dystonia were classified according to the criteria reported in Wiener and Lang (1989).

Apparatus

Arm movements were recorded by means of a two-joint articulated structure (Morasso, 1981) with one end of the structure fixed on a table. A handle, attached to the free end of the structure, slid over the table. Signals from two potentiometers, placed on the shafts of the mechanical joints, were recorded and then digitized at a sampling rate of 100 Hz, on an IBM compatible computer. Potentiometer data were collected for a 5 s period. Data were stored on floppy disks for subsequent analysis.

During testing, the subjects sat on a chair and grasped the handle of the structure. To minimize body movements, the subject's trunk was strapped to the chair and the wrist was splinted. The arm was suspended, so that elbow and shoulder joints were approximately at the same level on the horizontal plane. This positioning minimized changes in the position of the arm during the different trials and tasks. Such positioning also ensured that the forearm did not conceal the final vertex of the pentagon during drawing of the fifth segment in the counter-clockwise direction. The visibility was checked by the experimenter during the test.

Experimental paradigms

With the dominant arm, the subjects were instructed to trace different geometrical patterns marked on the table. Each pattern comprised a different number of segments (from two to five; *see* Fig. 1) and each segment was 17 cm long. The vertices of the segments were surrounded by a 1.5 cm diameter circle, which marked the boundary of the target zones for the end of each movement.

To study patients with Parkinson's disease, two main experimental paradigms were used. In Experiment A, four geometrical patterns with an increasing number of segments, made up to two, three, four and five (pentagon) segments were traced in a counter-clockwise direction. In Experiment B, first a pentagon was traced in a counter-clockwise and clockwise direction, starting from the same point and secondly each

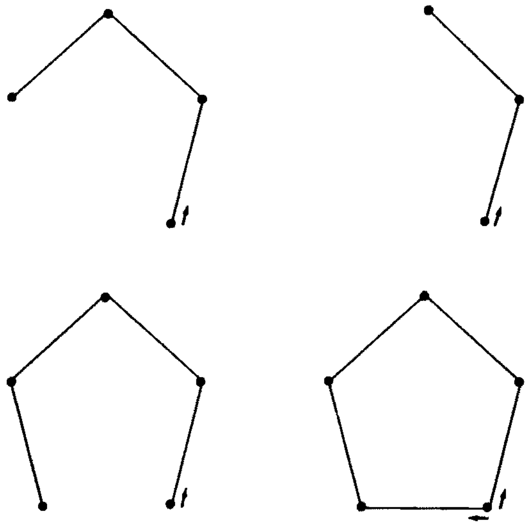

FIG. 1. Geometrical patterns used in Experiment A and B1 The arrows indicate the starting-point and the direction of the movements. The two arrows indicate that the pentagon was drawn in a counter-clockwise and clockwise direction. Each vertex was enclosed in a circle with a diameter of 1.5 cm

segment of the pentagon was traced singly in a counter-clockwise direction. Patients with Huntington's disease and dystonia participated only in Experiment B. In all the experiments, the different patterns were presented in random order.

The subjects were instructed to trace each segment of the geometrical patterns as fast as possible and stop near the vertices. When the geometrical patterns had to be traced sequentially, the subjects were also told to start the subsequent tracing movement as soon as possible. They moved after a verbal command of 'go', without being made to hurry. Before data collection started, normal subjects and patients practised the movements. The data from 10 movements were collected for each task. Trials in which the subjects failed to reach the vertices accurately enough were excluded. The subjects rested for 20–30 s between each movement, and for 2–3 min between the various motor tasks. Normal subjects and patients with Parkinson's disease participated in Experiments A and B on different days. Patients with Huntington's disease and dystonia performed Experiment B on one day.

Movement time (MT) for each segment of the patterns was measured with a cursor by visual inspection of hand velocity. The beginning of a movement was defined as the point when hand velocity reached and then stayed over the arbitrary value of 200 mm/s for a least 50 ms. In both normal subjects and patients, slight oscillations of the hand around the vertices often made it difficult to determine the end of the movement. The end of the movement was therefore taken as the moment when velocity fell below 200 mm/s for the first time. For the sequential tasks in Experiment B, we also measured the time elapsing between the end of one segment and the start of the next (pause). The coefficient of variation of MT was calculated during the execution of a pentagon in a clockwise and a counter-clockwise direction (Experiment B1).

Statistical analysis

Intergroup differences were tested with a one-way analysis of variance (ANOVA). Regression analysis was used to investigate intragroup relationships between movement parameters and the position of the segments in the sequential tasks and relationships between movement parameters and age in the normal subjects. Finally, in Parkinson's disease the possible increase in MT during the execution of the motor sequences was further tested by computing the within-subject regression. Intragroup differences in the slope and intercept were then compared with a one-way ANOVA.

RESULTS

Normal subjects

All the normal subjects were able to perform the tasks. As controls we used two groups of normal subjects of different ages (the younger group for the dystonic patients and the older group for the patients with Parkinson's and Huntington's diseases). Data from Experiment B (*see* Patients and methods) were used to see whether movement parameters and age of normal subjects were correlated. For each subject we calculated the mean value of four parameters: (i) the MTs obtained when each segment was traced singly in a counter-clockwise direction; (ii) the MTs obtained when the pentagon was traced in a counter-clockwise direction; (iii) the pauses obtained when the pentagon was traced sequentially in a counter-clockwise direction; (iv) the differences between segmental MT obtained during sequential and single movements (this parameter was used as a measure of slowness in MT due to the sequential nature of the complex motor task). We found that only MT during single ($r = 0.781$; $P < 0.005$) and sequential ($r = 0.863$; $P < 0.001$) tasks correlated positively with age. Because the aim of the study concerns changes in pathological states, we will not discuss movement changes attributable to age further.

Parkinson's disease patients

All the patients were able to perform all the movements according to the instructions.

Experiment A: two- to five-sided geometrical figures traced in a counter-clockwise direction. The patients took longer than the normal subjects to execute each segment of the geometrical patterns (Table 4). An ANOVA (performed separately for each data set) revealed a significant intergroup difference for the two-sided ($P < 0.0005$), three-sided ($P < 0.001$), four-sided ($P < 0.0001$) and five-sided ($P < 0.0005$) patterns. To investigate whether the MT lengthened as the performance of a motor sequence progressed we correlated the MT of the various segments and the position of the segments in the sequential task. No significant correlation was found in the normal subjects. In sharp contrast, on completing the sequence all the patients showed a prolonged MT

TABLE 4 MOVEMENT TIMES IN NORMAL SUBJECTS AND PATIENTS WITH PARKINSON'S DISEASE

	Two-sided pattern		*Three-sided pattern*		*Four-sided pattern*		*Five-sided pattern*	
	N	*P*	*N*	*P*	*N*	*P*	*N*	*P*
Side 1	276.5 ± 21.3	335.9 ± 17.5	274.3 ± 24.2	336.1 ± 21.8	279.3 ± 22.0	324.7 ± 21.1	290.7 ± 23.5	343.0 ± 19.9
Side 2	293.0 ± 11.8	371.8 ± 15.9	291.8 ± 17.4	360.8 ± 17.3	301.3 ± 18.4	363.6 ± 21.6	298.4 ± 21.8	372.9 ± 20.5
Side 3	–	–	313.4 ± 25.1	379.3 ± 20.1	296.8 ± 28.5	369.2 ± 22.3	321.7 ± 27.9	383.4 ± 20.5
Side 4	–	–	–	–	288.6 ± 22.6	394.3 ± 26.6	311.1 ± 22.4	391.6 ± 24.8
Side 5	–	–	–	–	–	–	299.0 ± 25.2	422.9 ± 26.5

Movement times in milliseconds for tracing different geometrical patterns in patients with Parkinson's disease (P) and in normal subjects (N). Values are means ± 1 SE. Differences between normal subjects and patients were significant for all the geometrical patterns tested (ANOVA).

and a significant correlation was found in the patients' performance for the four-sided ($r = 0.289$; $P < 0.05$) and the five-sided ($r = 0.295$; $P < 0.05$) geometrical patterns. That is, in these tasks, as the execution of the sequences progressed, MTs for the segments lengthened.

For the four-sided pattern, the within-subject regression analysis yielded a mean function of $y = 2.35x+285.6$ in normal subjects and of $y = 22.05x+308.6$ in the patients. For the five-sided pattern the mean function was $y = 1.29x+323.1$ in the normal subjects and $y = 17.81x+329.6$ in the patients. The slope for both patterns was significantly higher in the patients than in normal subjects ($P < 0.001$), whereas the intercept was similar in the two groups. In other words, the slope was much steeper in the patients than it was in normal subjects.

Experiment B1: comparison between the pentagon traced in a counter-clockwise and clockwise direction. The aim of this experiment was to see whether the increase in MT seen as the sequence progressed was due to the different positions of the segments in the workspace or to the direction of the movements. Patients were significantly slower than normal subjects (counter-clockwise task: $P < 0.0001$; clockwise task: $P < 0.0001$). In the patients, but not in normal subjects, the MT for the later segments of the sequence increased in both clockwise and counter-clockwise tasks (Table 5). In the patients, correlation between MTs and the position of the segments in the sequences reached a significant level when the task was performed in a counter-clockwise direction ($r = 0.275$; $P < 0.05$), and was not statistically significant when the task was performed in a clockwise direction ($r = 0.195$). For the counter-clockwise task the within-subject regression analysis showed a mean function of $y = 1.26x+323.19$ in the normal subjects and of $y = 15.3x+345.5$ in the patients. For the clockwise task the mean function was $y = -0.62x+329.3$ in normal subjects and $y = 9.31x+359.01$ in the patients. The slope for both tasks was significantly steeper in the patients ($P < 0.005$ for the counter-clockwise and $P < 0.05$ for the clockwise task), whereas the intercept was similar in

TABLE 5 MOVEMENT TIMES IN NORMAL SUBJECTS AND PATIENTS WITH PARKINSON'S AND HUNTINGTON'S DISEASE

	Pentagon traced in a counter-clockwise direction			*Pentagon traced in a clockwise direction*		
	N	*P*	*C*	*N*	*P*	*C*
Side 1	315.3± 19.7	352.3± 18.3	418.6± 46.9	314.5± 23.5	363 3± 14 8	399.3± 29.3
Side 2	329.8± 19.6	388.0± 17.4	391.1± 24 8	345.1± 27.2	380.7± 17 4	399.8± 31.0
Side 3	339.5± 23.7	395.9± 20.0	406 2± 32 2	323.0± 23 7	386.8± 19.6	390.2± 27.7
Side 4	327.2± 17.6	396.2± 22.5	393.4± 30.2	340.8± 18.1	407.4± 17.6	424.1± 32.8
Side 5	322 9± 19 0	424.7± 24 4	400 1± 27 2	313.6± 23.3	396 6± 21.0	366 8± 33 1

Movement times (in milliseconds) for tracing a pentagon in a clockwise and a counter-clockwise direction in normal subjects (N), and in parkinsonian (P) and choreic (C) patients. Values are means ± 1 SE. Differences between normal subjects and patients were significant for both tasks (ANOVA) both groups. Again, this means that the slope was steeper in the patients than in normal subjects.

Figure 2 shows the coefficient of variation of MTs during the counter-clockwise task.

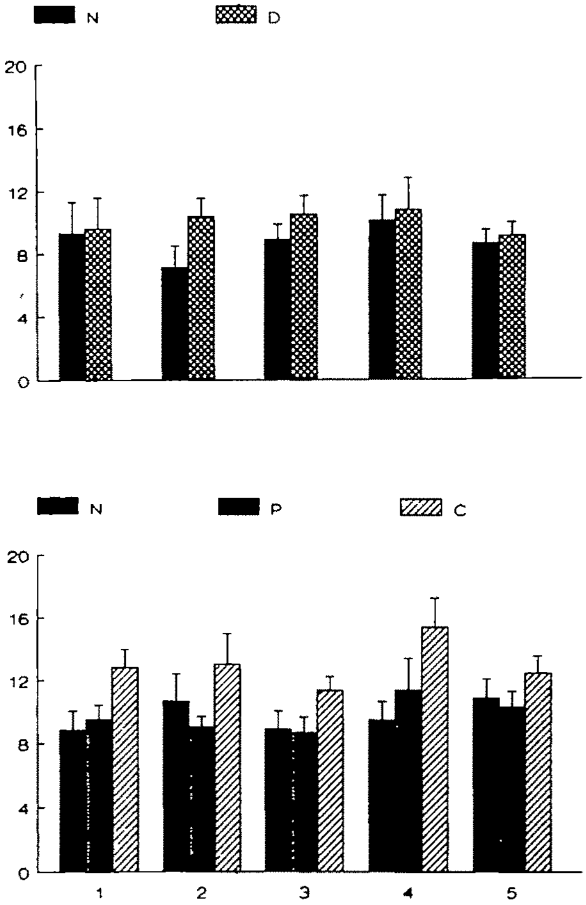

FIG. 2. Coefficient of variation of MT during the drawing of the pentagon in a counter-clockwise direction The numbers on the horizontal axes indicate the sides of the pentagon, those on the vertical axes indicate the coefficient of variation Data from age-matched normal subjects (N) and dystonic patients (D) are shown in the upper panel; those from age-matched normal subjects (N), parkinsonian (P) and choreic (C) patients appear in the lower panel. Each bar represents the mean ± 1 SE

The coefficient was similar in both groups. Data from the clockwise task were similar to those from the counter-clockwise task.

Table 6 shows the pauses for the pentagon traced in a counter-clockwise and clockwise manner. In both tasks, the pauses were longer in the patients than in the normal subjects (counter-clockwise task; $P < 0.0001$; clockwise task $P < 0.0001$). Correlations between

TABLE 6 PAUSES IN NORMAL SUBJECTS AND PATIENTS WITH PARKINSON'S AND HUNTINGTON'S DISEASE

	Pentagon traced in a counter-clockwise direction			*Pentagon traced in a clockwise direction*		
	N	*P*	*C*	*N*	*P*	*C*
Pause 1	173.2± 24.3	273.6± 31.5	294.9± 49.6	145.2± 20.3	222.3± 19.7	280.7± 50.4
Pause 2	139.6± 21.0	224.7± 26.9	278.1± 61.9	113.6± 16.1	191.1± 15.6	264.5± 50.3
Pause 3	131.9± 14.3	208.9± 23.7	293.4± 58.6	133.9± 22.1	228.6± 14.9	332.9± 64.0
Pause 4	134.1± 22.2	223.2± 25.2	266.5± 51.8	166.2± 25.8	238.6± 21.1	358.4± 82.0

Pauses (in milliseconds) during the tracing of a pentagon in a clockwise and a counter-clockwise direction in normal subjects (N), and in parkinsonian (P) and choreic patients (C). Values are means ±1 SE. Differences between normal subjects and patients were significant for both tasks (ANOVA).

pauses and their position in the sequence were not significant in either the normal or parkinsonian subjects.

Experiment B2: comparison between segments traced during the sequence and those traced singly. To investigate further the possible contribution of space, we also computed the difference between MTs obtained during the sequential task and those obtained when each segment was traced singly. We believe that this difference quantifies the slowness ascribable to the sequential nature of the complex task. Figure 3 shows that the difference was larger in the patients than in normal subjects ($P < 0.05$). The correlation between this extra time and the position of the segments in the sequence did not reach a significant level in patients ($r = 0.227$, $P < 0.059$) or in normal subjects ($r = 0.0157$). The within-subject regression analysis showed a mean function of $y = 0.34x+21.98$ in the normal subjects and of $y = 7.85x+21.43$ in the patients. No significant difference was found when the slope and intercept were considered.

Huntington's disease patients

All the patients were able to perform the task. Four patients out of nine were taking neuroleptic drugs. Movement parameters were similar in the two subgroups of patients.

Experiment B1: comparison between the pentagon traced in a counter-clockwise and clockwise direction. In the counter-clockwise ($P < 0.0001$) and in the clockwise task ($P < 0.0005$) MT was longer than it was in normal subjects (Table 5). No statistically significant correlation was found between MT and the position of the segments in the sequences; that is, progressive execution of the sequences had no effect on MT.

Figure 2 shows the coefficient of variation of MTs during the counter-clockwise task. The coefficient was higher in the patients than in normal subjects ($P < 0.0005$). Data from the clockwise task were similar to those from the counter-clockwise task.

The pauses were longer in the patients (counter-clockwise task $P < 0.0001$; clockwise task $P < 0.0001$) than in normal subjects (Table 6). No statistically significant correlation was found between the pauses and their position in the sequence.

Experiment B2: comparison between segments traced during the sequence and those traced singly in a counter-clockwise direction. Figure 3 shows the difference between

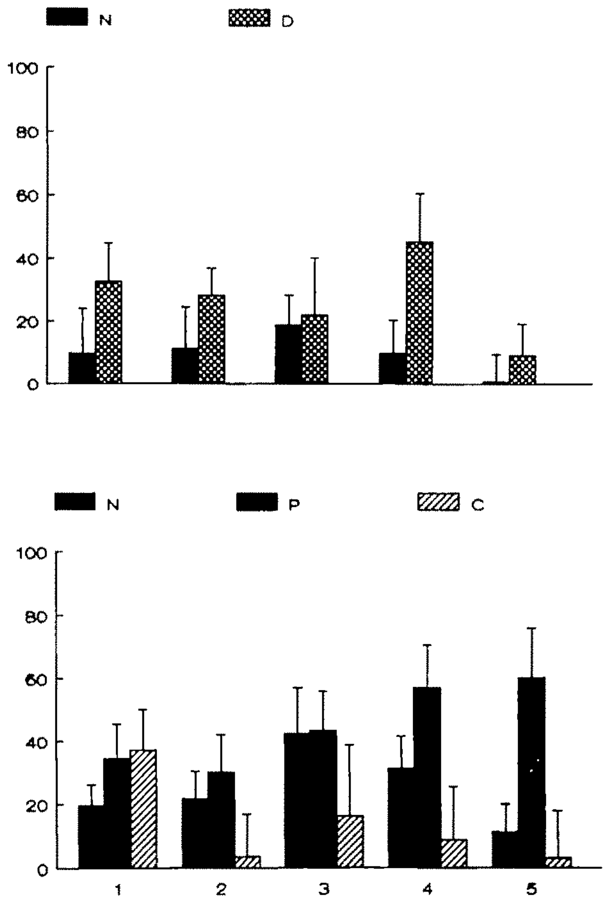

Fig 3 Differences between MTs obtained during the drawing of the pentagon in a counter-clockwise direction and those obtained when each side was traced singly in the same direction The numbers on the horizontal axes indicate the sides of the pentagon; those on the vertical axes indicate the differences in milliseconds. Data from age-matched normal subjects (N) and dystonic patients (D) are shown in the upper panel, those from age-matched normal subjects (N), parkinsonian (P) and choreic (C) patients appear in the lower panel

MTs for the execution of the sequence and the single segments. These results were similar in Huntington's disease patients and normal subjects. Furthermore, the differences did not correlate significantly with the position of the sides in the sequence.

Dystonic patients

All the patients were able to perform the motor tasks according to the instructions. Four of the seven patients were taking anticholinergic drugs. Movement parameters were similar in the two subgroups of dystonic patients.

Experiment B1: comparison between the pentagon traced in a counter-clockwise and clockwise direction. In both tasks (counter-clockwise task $P < 0.0001$; clockwise task $P < 0.0001$) MTs were longer than they were in normal subjects (Table 7) and no

TABLE 7. MOVEMENT TIMES AND PAUSES IN NORMAL SUBJECTS AND PATIENTS WITH DYSTONIA

	Pentagon traced in a counter-clockwise direction		*Pentagon traced in a clockwise direction*	
	N	*D*	*N*	*D*
Side 1	232.4 ± 11.1	349.0 ± 43.7	234.0 ± 12.7	349.8 ± 33.3
Pause 1	142.0 ± 31.4	220.1 ± 46.4	117.0 ± 22.4	219.9 ± 48.9
Side 2	263.4 ± 11.4	366.6 ± 37.2	247.6 ± 8.8	356.5 ± 40.8
Pause 2	139.4 ± 25.1	219.9 ± 48.7	131.6 ± 19.6	212.9 ± 41.2
Side 3	256.0 ± 10.6	371.3 ± 44.5	246.2 ± 5.9	370.4 ± 44.0
Pause 3	126.8 ± 17.0	221.7 ± 47.4	128.8 ± 8.5	222.5 ± 40.7
Side 4	244.2 ± 12.1	362.8 ± 41.8	283.4 ± 10.4	385.0 ± 38.9
Pause 4	125.2 ± 15.3	210.5 ± 48.5	100.0 ± 12.9	207.2 ± 47.2
Side 5	249.2 ± 11.3	344.0 ± 37.3	235.2 ± 14.9	364.4 ± 48.1

Movement times and pauses (milliseconds) during tracing of a pentagon in a clockwise and a counter-clockwise direction in normal subjects (N) and patients with dystonia (D) Values are means ± 1 SE. Differences between normal subjects and patients were significant (ANOVA test).

statistically significant correlation was found between MT and the position of the segments in the sequence.

Figure 2 shows the coefficient of variation of MT during the counter-clockwise task. The coefficient was similar in both groups. Data from the clockwise task were similar to those from the counter-clockwise task.

Pauses were also significantly prolonged in the patients (counter-clockwise task $P < 0.001$; clockwise task $P < 0.0005$). No significant correlation was found between movement parameters and position of the segments and vertices in the sequence.

Experiment B2: comparison between segments traced during the sequence and those traced singly in a counter-clockwise direction. Figure 3 shows the difference between the MTs obtained during the execution of the pentagon and the MTs for the segments performed singly. This difference was larger in the patients ($P < 0.05$). No significant correlation was found with the position of the segments in the sequence.

DISCUSSION

Our first observation was that the Parkinson's disease patients took longer than normal subjects to execute the single segments and the entire geometric figure. This confirms observations that these patients perform simple and complex arm movements slowly. When patients with Parkinson's disease had to trace geometrical patterns with an increasing number of sides, the MT became longer as the execution of the sequence progressed. One possible explanation for this phenomenon could be the different position in the workspace of the segments of the geometric figures that had to be traced. In tracing the geometrical figures, elbow and shoulder joints needed to be activated differently. Tracing movements for sides 1 and 4 usually required predominant excursions at the elbow joint, whereas those at the shoulder were less evident. By contrast, shoulder excursions were more evident during the tracing of sides 2 and 3, and became predominant during the tracing of side 5. The direction of the tracing movements is also important. Recent studies (Crutcher and DeLong, 1984; Crutcher and Alexander, 1990) have documented that striatal neurons are involved in coding movement direction, even when this aspect is dissociated from the need to generate muscle force. The 'spatial' aspects of the task may therefore have concurred to some degree in determining the progressive MT lengthening seen in these patients as the sequence was completed. In patients with Parkinson's disease, the progressive increase in MT in the motor sequence was evident during the counter-clockwise and clockwise tasks. Correlation between MT and the position of the segments in the sequence was statistically significant only for the counter-clockwise task, but within-subject regression analysis showed that for both tasks the slope was significantly steeper in parkinsonian than in normal subjects. Differences between MTs obtained during the sequential task and those obtained when each segment was traced singly, quantify the slowness related to the sequential nature of the complex task, ruling out the other causes of bradykinesia. Such differences were larger in the patients than in normal subjects; in the patients the differences were also larger for the later segments in the sequence. Correlation between the differences and the position of the segments in the sequence, however, did not reach a statistically significant level in either group. Neither did the two groups differ in their slope and intercept. These results suggest that during the sequential movements, the 'spatial' aspects of the tasks possibly concurred in determining the progressive lengthening of MTs.

Studying the ability of patients with Parkinson's disease in drawing triangles and squares on a writing table, Berardelli *et al.* (1986*a*) found that the pauses at the angles of the geometric figures were prolonged. Similar conclusions were reached by Benecke *et al.* (1987) in their study of two-step sequential movements, such as flexing the elbow and squeezing a force transducer with the hand. The prolongation of pauses was thought to reflect a difficulty in switching from one motor program to another. We have now shown that the prolonged pauses at the vertices, which represent difficulty in switching from one movement to the next, do not lengthen further as the execution of the sequence progresses.

In conclusion, in patients with Parkinson's disease complex arm movements are performed slowly, pauses are prolonged and the difference between MTs for complex and single tasks was abnormally large. Finally, as the performance of sequential arm movements progresses, MTs become longer. These abnormalities may not be detected in studies examining speech or other motor tasks performed without externally imposed spatial targets (Connor and Abbs, 1991).

In this study we found that Huntington's disease patients are slow in executing movements and switching from one movement to the next. Their performance varied more than that of normal subjects. Similar results were obtained by Thompson *et al.* (1988), who used a sequential task of squeezing the hand and flexing the elbow. We found that the differences between MTs during the sequential task and those obtained when each segment was traced singly were comparable to those in normal subjects. Thus the performance of the sequence did not produce a further slowness of motor execution. Differences in the motor tasks examined and selection of patients might explain why Thompson *et al.* (1988) obtained different results. Finally, MTs did not lengthen as the performance of sequential arm movement progressed.

Our results in dystonic patients constitute the first description of an impairment of sequential movements in dystonia. Van der Kamp *et al.* (1989) showed that dystonic patients are slow in executing simple rapid elbow movements. We now show that during a sequential task dystonic patients are slow in executing movements and switching from one movement to the next. Performance of the sequential task also revealed a further slowness of movement execution over the single task paradigm, but not lengthening of MTs as the sequence progressed.

The difficulty in executing complex arm movements, i.e. slow movements and prolonged pauses, shared by the patients with Parkinson's disease, Huntington's chorea and dystonia in this study suggests that bradykinesia and difficulty in switching from one movement to the next during complex movements are common abnormalities in basal ganglia disease. However, parkinsonian patients, but not choreic and dystonic patients, had an additional abnormality: progression of a motor sequence lengthened MTs. It is unlikely that in choreic and dystonic patients this phenomenon was not detected because it was obscured by an increased variability of MTs. Although conceivable in patients with Huntington's disease, this is highly improbable in our patients with dystonia, who showed normal movement variability.

In patients with Parkinson's disease, Hallett and Khoshbin (1980) have explained the bradykinesia of simple elbow flexion as due to a failure to 'energize' the agonist muscles appropriately. Further studies have shown that bradykinesia is due not to saturation of the first agonist burst but probably to an inappropriate scaling of the size of the first agonist burst to the movements to be performed (Berardelli *et al.*, 1986*b*). More recently, demonstrating that patients with Parkinson's disease are able to vary the duration of their movements with a temporal accuracy comparable to that of normal subjects, Teasdale *et al.* (1990) have suggested that slowness of movements varies as a function of task requirement and might be induced by increasing the spatial accuracy of the movement to be performed (*see also* Sanes, 1985). Sheridan and Flowers (1990) suggested that bradykinesia may partly result from 'the need for patients to monitor their movements in order to reduce variability to an acceptable level, rather than an inability to generate sufficient forces'.

Some of the mechanisms proposed for simple movement may possibly also underlie slowness in executing sequential movements. Observing that motor disturbances in Parkinson's disease are more pronounced in complex than in simple movements, Benecke *et al.* (1987) have suggested that abnormalities in sequential movements could be related to disturbed processing in the supplementary motor area. Studies in normal subjects (Roland *et al.*, 1980) and in patients with lesions of the supplementary motor area (Laplane *et al.*, 1977; Dick *et al.*, 1986; Gaymard *et al.*, 1990) have stressed the role of this area in sequencing motor acts. Furthermore, in monkeys, the supplementary motor area constitutes the major cortical target for the so-called basal ganglia motor loop (*cf* Alexander *et al.*, 1986). The most plausible reason for the impairment of sequential motor acts in patients with Parkinson's disease, Huntington's disease and dystonia thus appears to be related to an abnormal activation of the supplementary motor area.

Why did the bradykinesia in our Parkinson's disease patients worsen as the sequence progressed? One possibility is that the progressive slowing of limb movement in parkinsonian patients is due to problems other than motor. In the execution of complex motor tasks, cognitive factors such as arousal, motivation and selective attention certainly play a role. Talland and Schwab (1964) and Horne (1973) demonstrated that if a set of instructions was made more and more complex, without altering the motor aspects of the task, Parkinson's disease patients' performance deteriorated. In addition, even clinically non-demented Parkinson's disease patients may have some degree of cognitive impairment (Lees and Smith, 1983). Arguing against a major role of cognition in this respect is the observation that progressive lengthening of MT was not a feature of the Huntington's disease group. Yet these patients as well, have recognized cognitive defects (*see*, for example, Fisher *et al.*, 1983).

Another possibility concerns the ability of Parkinson's disease patients to store and hold motor programs (Marsden, 1989; Hallett, 1990), an ability that has been termed 'motor memory'. As time elapses, 'motor memory' may possibly deteriorate, causing movement execution to become more and more faulty. In parkinsonian patients, Labutta *et al.* (unpublished; cited in Hallett, 1990), studying single arm movements in a delayed response paradigm, found no abnormality within a delay of up to 8 s. In a recent study (Robertson and Flowers, 1990), a group of parkinsonian patients learned some sequential arm movements cued by light-emitting diodes. After a period of training, the patients reproduced the sequence correctly when the light-emitting diodes were off. The authors concluded that motor memory was unimpaired. Unfortunately, no information was provided about the MTs of the different steps composing the task. The question still needs to be addressed.

The progressive worsening of bradykinesia seen in this study may be related to the phenomenon of fatigue occurring in patients with Parkinson's disease during the execution of repetitive movements (Wilson, 1925; Schwab *et al.*, 1959). On the other hand, repetitive and sequential movements may have different physiological mechanisms and may be differently affected in Parkinson's disease (Harrington and Haaland, 1991).

Finally, Marsden (1989) has proposed that the progressive nature of the deficits in sequencing motor acts may imply that 'motor basal ganglia are more concerned with directing what happens to the next movement in a sequence than with the initial movement'. Namely, information processed by the basal ganglia is used by other motor areas, or at least concurs to select the correct parameters for the incoming movement. If such processing is faulty, then the final motor output is abnormal. So far, this hypothesis is not supported by direct experimental evidence.

The finding that sequential movements are slow in Parkinson's disease, Huntington's disease and dystonia fits the hypothesis that the basal ganglia are part of a cortico-cortical loop that maintains and reinforces ongoing motor behaviours (Penney and Young, 1986). Finally, the progressive lengthening of MT (present only in Parkinson's disease) suggests that nigro-striatal dopaminergic pathways are particularly important in reinforcing long motor sequences. The absence of this abnormality in choreic and dystonic patients agrees with recent observations on the inhomogeneous anatamical organization of basal ganglia (*cf* Penney and Young, 1986; Albin *et al.*, 1989).

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ANODAL AND CATHODAL STIMULATION OF THE UPPER-LIMB AREA OF THE HUMAN MOTOR CORTEX

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SUMMARY

In 18 neurologically normal subjects the corticofugal volleys evoked by anodal and cathodal electrical stimulation of the motor cortex were recorded using epidural electrodes at the high-thoracic and low-thoracic regions of the spinal cord during surgery for scoliosis. At and just above threshold, anodal and cathodal stimulation of the upper-limb area and motor cortex produced a D wave that propagated to the low-thoracic region. The stimulus intensity required to produce D waves was significantly lower with anodal stimulation. I waves were recorded at higher stimulus intensities than the D wave but not more readily with cathodal stimulation. There was no significant difference in the extent to which stimulus intensity had to be increased above D-wave threshold to produce I waves with the two stimulus polarities, and the number of I waves was the same when the stimulus was increased by the same amount above D-wave threshold. After withdrawal of isoflurane, I waves could not be recorded when the stimulus intensity was below D-wave threshold with either stimulus polarity. Anodal stimulation over the upper-limb area remained more effective than cathodal stimulation in producing both D and I waves. These results indicate that, at threshold, regardless of anaesthesia, anodal and cathodal stimuli access upper-limb corticospinal neurons directly at a similar site, the anodal stimuli being more effective. In addition, the results suggest that some corticospinal neurons in the upper-limb area of motor cortex have projections to lumbar segments.

INTRODUCTION

It is now more than a decade since it became feasible to stimulate the human motor cortex electrically through the scalp (Merton and Morton, 1980), but there are still uncertainties about the precise mechanisms through which the corticospinal system is activated (Amassian *et al.*, 1987). The uncertain mechanisms of activation have prompted detailed analyses of post-stimulus histograms (PSTHs) of voluntarily active motor units in response to transcranial stimulation of the human motor cortex using electrical and magnetic stimuli (Day *et al.*, 1987, 1989; Hess *et al.*, 1987). As a result, and by analogy with data on stimulation of exposed motor cortex of cat and monkey (Phillips and Porter, 1977), it has become accepted that transcranial anodal electrical stimulation using weak or modest stimulus intensities activates corticospinal neurons directly at the initial segment, so producing a short-latency volley termed the 'D wave'. With higher stimulus intensities corticospinal neurons may be activated indirectly, producing longer-latency volleys ('I waves'), due to stimulation of excitatory interneurons synapsing with the corticospinal neuron (Rothwell *et al.*, 1991). Transcranial cathodal stimulation is thought to produce

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I waves more readily than anodal stimulation, at a lower intensity relative to the threshold for the D wave (Day *et al.*, 1989). In addition, the PSTH data have supported the view that magnetic stimulation of the human motor cortex produces twitch contractions at longer latency than anodal electrical stimulation because, like cathodal stimulation, magnetic stimulation preferentially generates I waves rather than D waves in corticospinal axons.

Recent studies have questioned this unifying hypothesis. In recordings of corticofugal volleys from the the lower-limb area in anaesthetized human subjects, increasingly strong anodal electrical stimulation was found to activate corticofugal axons at progressively deeper sites to cerebral cortex, while cathodal stimulation activated corticofugal axons directly rather than indirectly (Burke *et al.*, 1990). However, the 'unifying hypothesis' was predicated on data for the upper-limb projection (Rothwell *et al.*, 1991), and no such claims have been advanced for the lower-limb projection. Indeed, because the orientation of corticospinal axons to the scalp surface differs for the upper- and lower-limb areas of human motor cortex, findings for the lower-limb projection may not be applicable to the upper-limb projection. In addition, anaesthesia is likely to have altered the corticospinal volleys, particularly the I waves, possibly producing a threshold difference for D and I waves that does not exist for the unanaesthetized alert subject. Nevertheless the concerns raised by Burke *et al.* (1990) are similar to those of Edgley *et al.* (1990), who demonstrated that, in the monkey, magnetic stimulation activated corticospinal axons directly, probably at the initial segment, while anodal electrical stimulation could activate corticospinal axons deep to motor cortex, even at the medullary pyramids. These findings contrast with those of Amassian *et al.* (1990), who found that the effects of magnetic stimulation of monkey motor cortex depended on coil orientation. However, with cathodal stimulation of the exposed cortex, they reported direct activation of corticospinal neurons, probably at the initial segment, in accordance with previous arguments (Amassian *et al.*, 1987) and with results of transcranial stimulation in patients undergoing surgery (Burke *et al.*, 1990), but at variance with reports in much previous literature (*see* Phillips and Porter, 1977).

The present study investigates the activation of corticospinal volleys by anodal and cathodal electrical stimuli delivered to the scalp of human subjects, addressing specifically the projection from the upper-limb area of motor cortex. The results indicate that when stimulating motor cortex through the intact scalp cathodal stimulation is merely a less effective method of activating the corticospinal system, and this is so regardless of anaesthesia. Evidence for a projection from the upper-limb cortex to lumbar segments is presented.

METHODS

Corticofugal volleys to transcranial electrical stimulation of the human motor cortex were recorded as part of monitoring spinal cord function in 18 patients undergoing surgery for scoliosis. None had clinical evidence of a central nervous system disorder though four suffered from Duchenne muscular dystrophy. The patients were aged 6–19 yrs, mean 13.4 yrs, 12 were female and six male. Informed consent was obtained from the patients and/or responsible relatives for the operative, anaesthetic and neurophysiological procedures, which had the approval of the institutional ethics committee.

The patients were anaesthetized with nitrous oxide and oxygen (70:30), isoflurane and fentanyl, paralysed using pancuronium and artificially ventilated. They lay prone throughout the operation. Recordings were made at the high-thoracic and low-thoracic regions of the spinal cord using bipolar electrodes inserted into the epidural space, as described previously (Burke *et al.*, 1990). The high-thoracic electrode was positioned to record corticofugal volleys to the upper limbs, the low-thoracic electrode those to the lower limbs.

Three silver-silver chloride cup electrodes were cemented to the cleaned but otherwise unprepared scalp with collodion and filled with electrode gel. One electrode was at the vertex, the second 7 cm lateral to the vertex over the upper-limb area (or 'hand' area) of motor cortex (Rothwell *et al.*, 1987) and the third 6 cm anterior to the second electrode. For stimulation of the upper-limb area the second and third electrodes were used. Electrical stimuli were delivered at intervals >3 s using an isolated stimulator with low output impedance (Digitimer D180A, Welwyn Garden City, Herts, UK), producing a capacitively coupled discharge (time constant 100 μs) that generally did not exceed 750 V. The evoked corticofugal volleys were recorded on a two-channel EMG/evoked potential machine (Medelec MS92B, Old Woking, Surrey, UK), as described previously (Burke *et al.*, 1990), using a bandpass of 500 Hz to 10 kHz. Duplicate averages, each of 10 or 25 responses, were obtained for each observation.

In six subjects, the inspired isoflurane was altered in steps, from the usual end-tidal concentration of 1–2%, allowing 5–10 min to elapse before a steady state was assumed. Adequate anaesthesia was maintained by nitrous oxide and fentanyl, so that there was no risk of the patient regaining consciousness. Blood pressure was monitored using an intra-arterial catheter: sodium nitroprusside was usually administered following cessation of isoflurane to maintain a constant arterial pressure within ±5 mmHg. Throughout each operation, core temperature was monitored at both oesophagus and tympanic membrane and kept constant at 34–35°C.

Data are quoted as mean ±SE. The significance of differences was assessed using analysis of variance and a two-tailed Student's *t* test for paired observations.

RESULTS

The effects of anodal and cathodal stimulation over the upper-limb area of the motor cortex were compared in 13 subjects, using electrodes 7 cm lateral to the vertex (over the upper-limb area) and 6 cm anterior to this site. With these montages, stimulus artefact was more prominent, and D and I waves were generally smaller and less well-defined than with the anode at the vertex and the cathode laterally over one upper-limb area (Fig. 1). Although the former montages are presumably more selective for upper-limb corticospinal projections (Rothwell *et al.*, 1987), corticospinal volleys were readily recorded at relatively low stimulus intensities at the high- and low-thoracic recording sites, as discussed below. The amplitude of I waves was usually <2 μV. Equally often with both anodal and cathodal stimulation, these small deflections contained a number of closely spaced peaks or consisted of a broad negative deflection in which individual subcomponents could still be recognized (Fig. 2). In one sequence the I waves were better seen in the low-thoracic recordings (Fig. 3), presumably because of a relatively poor signal-to-noise ratio for the high-thoracic recording such that the recovery from the stimulus artefact obscured the small I waves.

Effects of increasingly strong stimulation of the upper-limb area

In 11 subjects, stimulus intensity was increased in steps of 75 V from approximately 150 V, up to occasionally, 750 V. The size of the step thus corresponds to that used by Day *et al.*, 1989 (*see* their figs 8–11). With anodal stimulation, the D wave appeared at the high-thoracic site with a mean latency to the negative peak of 3.63 ms (SE ±0.16 ms) when the stimulus intensity was, on average, 269.3 V. With cathodal stimulation, the D wave appeared at this site at 3.66 ms (SE ±0.15 ms) when stimulus intensity was, on average, 334.1 V. The threshold intensity was lower in eight subjects

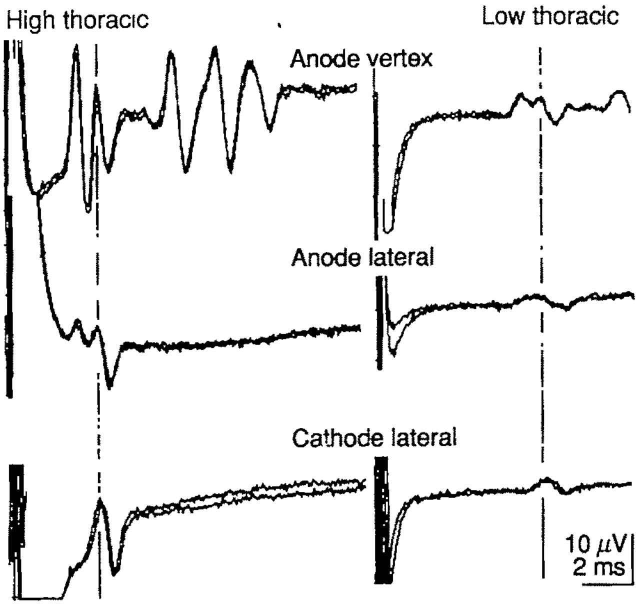

FIG 1. Different stimulus montages, with stimulus intensity of 450 V, after cessation of isoflurane (female, aged 13 yrs). Upper row: anode at vertex, cathode over upper-limb area: middle row: anode over upper-limb area, cathode 6 cm anteriorly; lower row: cathode over upper-limb area, anode 6 cm anteriorly. The vertical lines indicate the lowest-threshold component of the D wave at both recording sites. Note the short-latency D-wave components in the upper and middle rows. I waves are prominent in the upper row but not detectable with the other montages

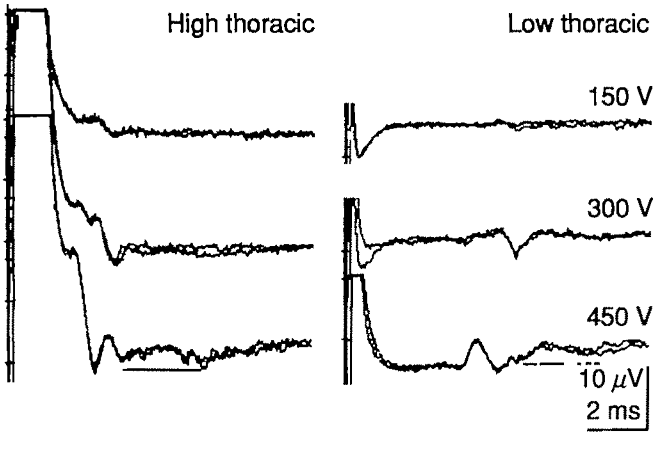

FIG. 2. Anodal stimulation of the upper-limb area (cathode 6 cm anterior) Isoflurane concentration 2%. Note the shift in the D wave at both recording sites as stimulus intensity was increased, and the prolonged I-wave activity (underlined), with poorly separated peaks.

with anodal stimulation and was the same in the remaining three. The difference in threshold (66.8 V) was significant ($P = 0.0126$; Table 1)..

With increasing stimulus intensity, the latency of the D wave decreased due to the

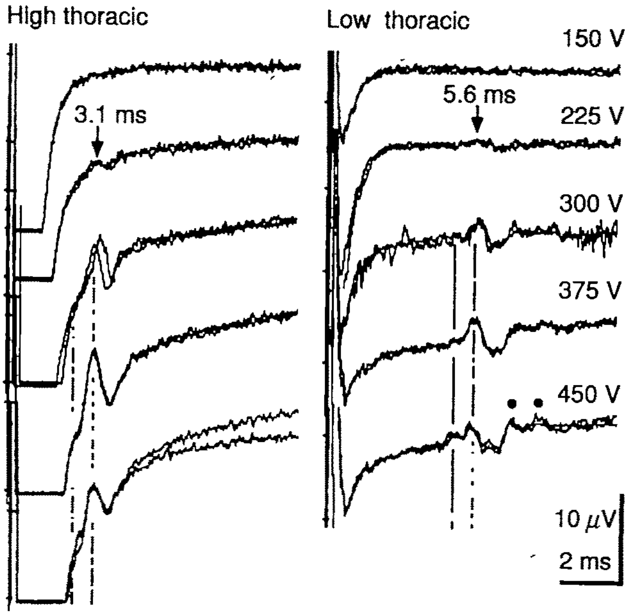

FIG. 3. Cathodal stimulation of the upper-limb area (anode 6 cm anterior) in the same subject as Fig. 2 (female, aged 14 yrs). Isoflurane concentration 2%. D waves appear at 225 V at both recording sites, and an early peak begins to appear in the D wave at 375 V. I waves are seen in the low-thoracic recording at 375 V and 450 V (filled circles) but not in the high-thoracic recording.

TABLE 1 THRESHOLDS FOR D AND I WAVES AT THE HIGH-THORACIC SITE

	n	*D wave (V)*	*I wave (V)*	*Difference (V)*
Anodal	11	269.3±25.6	336.1±33.2	66.8±16.0 (*P* = 0.002)
Cathodal	11	334.1±39.3	428.2±56.5	94.1±38.9 (*P* = 0.036)
Difference	11	64.8±21.4 (*P* = 0.0126)	92.1±36.5 (*P* = 0.0346)	27.3±36.5 (*P* = 0.472)

Results are given as mean ±SE

emergence of an earlier peak, indicating that axons were then stimulated at a more caudal level than at threshold. This occurred with both anodal and cathodal stimulation (Figs 2, 3). The onset and peak of the high-threshold short-latency D-wave peak was commonly obscured by artefact at the high-thoracic site (Fig. 3) but, when not, the conduction time between the high- and low-thoracic levels was the same as for the threshold volleys (Fig. 2). In some instances the high-threshold peak replaced the low-threshold peak (e.g. Fig. 2, right panels). However, intensities of up to 750 V did not produce a third higher-threshold shorter-latency peak in the D wave, as was seen in seven of 15 subjects using vertex anodal stimulation (Burke *et al.*, 1990).

I waves appeared when the intensity of anodal stimulation reached 336.1±33.2 V and the intensity of cathodal stimulation reached 428.2 ± 56.5 V (Table 1). For these measurements, the lowest stimulus intensity was noted, whether the threshold I waves were identified at the high-thoracic site (as was usual) or at the low-thoracic site (as was necessary for the data in Fig. 2). With both anodal and cathodal stimulation, the threshold intensity for I waves exceeded that for the D wave in eight subjects and was the same in three. The mean differences in threshold were statistically significant ($P = 0.002$ and 0.036, respectively; Table 1). The increases in stimulus intensity above D-wave threshold necessary to produce I waves (94.1 V with cathodal stimulation and 66.8 V with anodal stimulation) were not significantly different ($P = 0.472$): i.e. I waves were *not* relatively more easy to elicit with cathodal stimulation.

For the same stimulus intensity the number of I waves was greater with anodal stimulation. The strongest stimulus level used for both anodal and cathodal stimulation was, on average, 516 V, and at this common stimulus level there were, on average, 2.8 I waves/subject with anodal stimulation and 1.9 I waves/subject with cathodal stimulation, a difference that is significant ($P = 0.021$). However, when the number of I waves was counted at a fixed stimulus intensity above the relevant D-wave threshold, the same number of I waves occurred with anodal and cathodal stimulation: at, on average, 246 V above D-wave threshold, there were 2.3 I waves/subject with anodal stimulation and 2.2 I waves/subject with cathodal stimulation. These findings suggest that the main difference between anodal and cathodal stimulation of the upper-limb area is merely that cathodal stimulation is a less effective method of delivering current to the motor cortex. The findings provide no support for the view that the site of corticospinal activation is different with anodal and cathodal stimulation at any stimulus intensity.

Anaesthetic effects on I-wave thresholds produced by stimulation over the upper-limb area

In six subjects, the upper-limb area of the motor cortex was stimulated during and after withdrawal of isoflurane. Cathodal stimulation did not produce I waves at lower intensities than the D wave even when the isoflurane level was 0% (Figs 1, 4). In one subject a single I wave appeared at the same stimulus intensity (225 V) as the D wave (but this was also the case for three of 11 subjects in Table 1 when receiving isoflurane, *see* earlier). Figure 4 (left panel) shows the effects of increasing cathodal stimulation after withdrawal of isoflurane: there was a 20 μV D-wave at 450 V but I-wave threshold was 600 V.

When assessed using the same stimulus intensity in the same subjects, anodal stimulation produced more I-wave activity than cathodal after withdrawal of isoflurane. As shown in Fig. 4, anodal and cathodal stimulation at 450 V produced a D wave of some 20 μV. However, while anodal stimulation produced three I waves, cathodal stimulation produced none. The traces with vertex anodal stimulation confirm that the low-threshold deflection with stimulation of the upper-limb area was indeed the D wave, and this is supported by the short latency of the wave (2.8 ms to peak).

Corticofugal volleys recorded at the low-thoracic site

As illustrated in Figs 2, 3, 5, corticospinal volleys appeared at the low-thoracic site when the intensity of stimulation was quite low (Fig. 2, anodal, 150 V; Fig. 3, cathodal, 225 V; Fig. 5, cathodal, 375 V and anodal 300 V). In 10 subjects the thresholds for

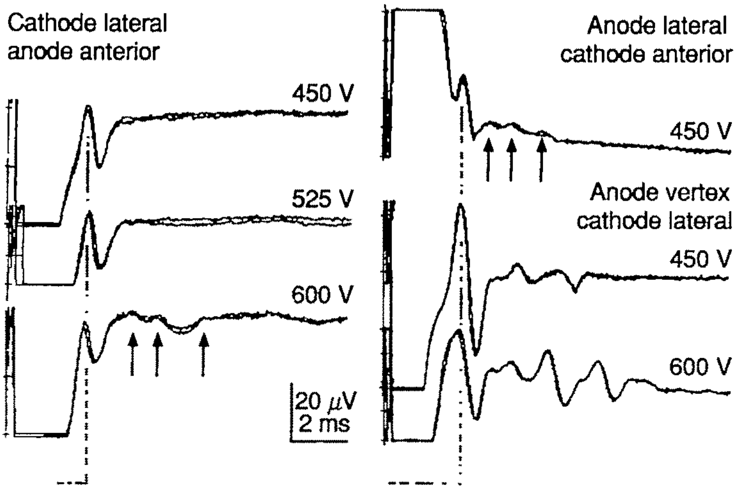

FIG. 4. I waves after withdrawal of isoflurane (female, aged 13 yrs). All recordings from the high-thoracic site. Left traces: increasing intensity of cathodal stimulation of upper-limb area. Note that I waves do not appear until 600 V (vertical arrows) Right traces: anodal stimulation over the upper-limb area (upper trace) and at the vertex (lower two traces) after withdrawal of isoflurane. Note that I waves are present with anodal stimulation at 450 V (vertical arrows).

the D wave could be determined for both recording sites using anodal and cathodal stimulation (Table 2). In four subjects with each stimulation montage the D-wave thresholds were identical for the two sites (Figs 2, 3) and in six the thresholds were slightly higher for the low-thoracic recordings (Fig. 5). The mean difference in threshold was less than the difference in threshold for D and I waves (*see* Table 1) and less than the difference in threshold for anodal and cathodal stimulation (Table 2). In addition, the conduction time between the high- and low-thoracic sites was the same in each subject as the conduction time for the volley set up by anodal stimulation of the vertex (Figs 1, 5).

It is possible that the higher threshold for the D wave at the more caudal site resulted from the smaller D-wave amplitude and, consequently, the poorer signal-to-noise ratio for that site. If so, these findings indicate that corticospinal axons projecting to the lower limbs will be activated whenever stimulation of the upper-limb area generates a significant corticospinal volley.

DISCUSSION

In the present study we have investigated anodal and cathodal stimulation of the upper-limb area of the human motor cortex, and come to conclusions similar to those in an earlier study on the lower-limb projection (Burke *et al.*, 1990). These results could not have been predicted because the orientation of corticospinal neurons and their axons to the surface and thereby to the current path is likely to differ for the upper-limb and lower-limb areas of the human motor cortex. In addition, there are two novel findings in the present study: first, the lower threshold for D waves than for I waves with cathodal stimulation cannot be attributed to the use of volatile anaesthetics and, secondly, corticofugal axons directed to the lower limbs are activated by stimulation over the upper-limb area.

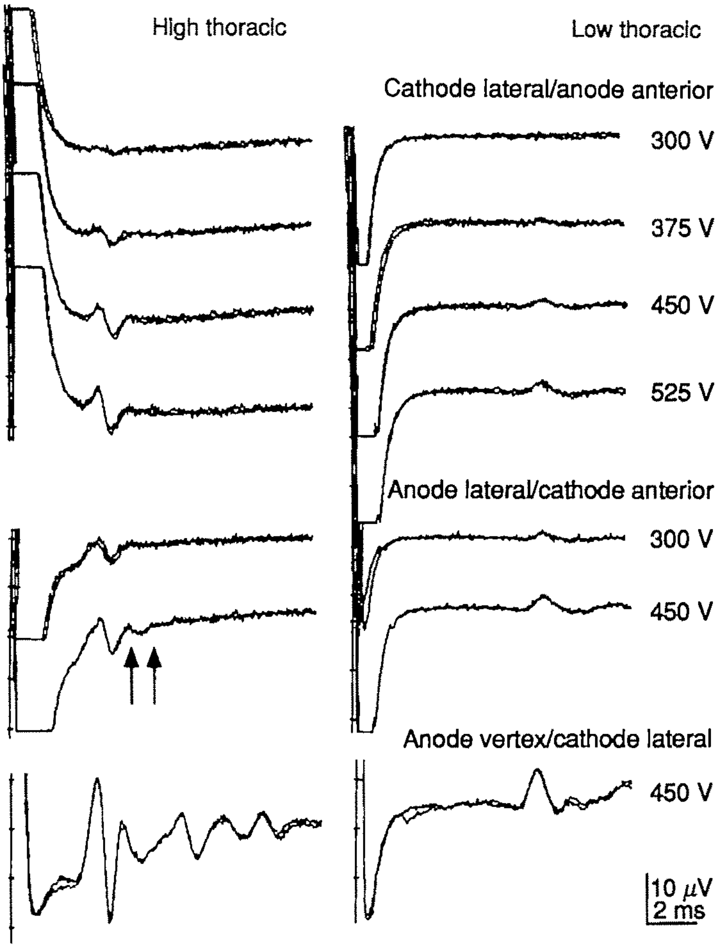

FIG. 5. Comparison of recordings from high- and low-thoracic sites with different stimulus montages Isoflurane concentration 2% (female, aged 16 yrs) Upper traces; cathodal stimulation of the upper-limb area produces a D wave at both sites with only slightly higher threshold for the low-thoracic site No I waves occur at up to 525 V. Middle traces: anodal stimulation of the upper-limb area produces a larger D wave for the same intensity but with same latencies, and with small I waves at 450 V (vertical arrows). Lower traces; vertex anodal stimulation produces a large D wave followed by a series of I waves The large D wave has similar (but slightly shorter) peak latencies but the same conduction time between recording sites

TABLE 2. THRESHOLDS FOR D WAVES AT HIGH- AND LOW-THORACIC SITES

	n	*High thoracic (V)*	*Low thoracic (V)*	*Difference (V)*
Anodal	10	281.3±33.6	317.3±39.3	36.0±11.5 (*P* = 0.0118)
Cathodal	10	330.0±44.7	382.5±51.8	52.5±18.7 (*P* = 0.0205)
Difference	10	48.8±19.2 (*P* = 0.0318)	65.3±23.4 (*P* = 0.0209)	

Results are given as mean ±SE.

Corticofugal volleys set up by electrical stimulation

It is an assumption that the corticofugal volleys recorded in the present study are in corticospinal axons. This assumption is probably soundly based for relatively weak stimulus intensities but not when the stimulus intensity is sufficient to activate corticospinal axons at deep sites, as it can do in monkey and man (Burke *et al.*, 1990; Edgley *et al.*, 1990). At high stimulus intensities, D-wave latency shortened but had the same conduction time between the two recording sites as at threshold, as also did many of the I waves. However, some of the late deflections not identifiable at both recording sites may have been not I waves in corticospinal axons but volleys in non-corticospinal axons. This possibility would not alter the conclusion that, regardless of anaesthetic level, both anodal stimulation and cathodal stimulation of the upper-limb area of the motor cortex activate corticospinal axons directly, and that neither preferentially generates I waves.

The present study provides no insight into the site of initiation of liminal D waves, except that the latencies are consistent with initiation at or near the initial segment of the corticospinal neuron. Given their identical latencies, anodal and cathodal D waves are likely to arise from the same site. Recently, it has been shown that liminal D waves are very sensitive to the changes in motor cortex excitability associated with changing levels of volatile anaesthetics (Hicks *et al.*, 1992). This sensitivity implies a site of initiation close to the initial segment.

It is noteworthy that there was no obligatory sequence of I-wave appearance: in any one subject different stimulating montages could produce a different sequence of I waves (Figs 4, 5), as might be expected if the direction of current flow was altered. As seen in this study, I waves were generally discrete short volleys occurring at reproducible latencies after the D wave. The broad I wave in Fig. 2 was thus atypical: presumably it resulted from overlapping activity of a number of small closely spaced I waves and, indeed, subcomponents can be readily identified in the high-thoracic recording.

If the repetitive firings of corticospinal axons that can follow direct activation are not tightly synchronized to the stimulus pulse, the averaging procedure used in the present study might have failed to demonstrate late volleys (Amassian *et al.*, 1990). Presumably any such activity would still have a significant effect on spinal motor neurons. However, for a PSTH to reveal increases in motor unit discharge at discrete latency intervals after stimulation of the motor cortex, as in the experiments of Day *et al.* (1989), it would require a synchronized excitatory postsynaptic potential in the relevant motor neuron and would therefore require the type of volley detectable in the present study. Nevertheless, it must be conceded that averaged traces may not define all I-wave activity, as was the case in the recording from the high-thoracic site in Fig. 2, and this is more likely with bipolar recordings (Amassian *et al.*, 1987, 1990).

Even allowing for the uncertainties discussed above, the present results reinforce the view that the differences between the effects of transcranial anodal and cathodal electrical stimulation are not due to a different mechanism of generating corticospinal volleys. Instead, the results suggest that cathodal stimulation is merely a less effective means of delivering current to the motor cortex, whether the subject is receiving volatile anaesthetics or not. Indeed, when stimulus levels were referred to D-wave threshold, cathodal stimuli proved to be as effective as anodal stimuli in producing I waves. The lower stimulus intensities required to produce corticospinal volleys with anodal stimulation is consistent with many previous studies, both in primates (*see* Phillips and Porter, 1977) and in human subjects (e.g. Day *et al.*, 1987, 1989; Rothwell *et al.*, 1987, 1991). Presumably the relevant corticospinal neurons occur largely along the convexity of the gyrus such that they have a perpendicular orientation to the scalp surface. This orientation to the surface would favour hyperpolarization of the dendrites and depolarization of the axon with anodal stimulation, and vice versa with cathodal stimulation (Phillips and Porter, 1977). Thus, the threshold for a propagated impluse would tend to be lower with anodal stimuli.

Reconciliation of the present results with PSTH data

Based on PSTHs of voluntarily active motor units innervating the human hand, Day *et al.* (1989) have suggested that, at threshold, transcranial cathodal stimulation is more likely to generate I waves than anodal stimulation, at least when I-wave threshold is referred to D-wave threshold. This represents an important difference between their study and the present, but this difference should not obscure the similarities. The findings with graded anodal stimulation and its greater efficacy in generating corticospinal volleys are precisely as predicted by Day *et al.* (1989). It is only in the pattern of the cathodal volley at and just above threshold that views diverge, and at least two methodological differences could have been responsible.

First, Day *et al.* (1989) inferred the occurrence of D and I waves from peaks of discharge in PSTHs of voluntarily active motor units. Multiple peaks in a PSTH do not necessarily mean multiple descending volleys. Their interpretation is supported by recordings of multiple volleys in the present study and other papers (*see* Rothwell *et al.*, 1991, for review), but the occurrence of multiple descending volleys does not exclude other factors from contributing to the PSTH. For example, multiple peaks in a PSTH could result from indirect corticofugal activation of motor neurons via interneurons or propriospinal systems, with secure transmission to the motor neuron pool more likely in the presence of the background voluntary contraction. Indeed, the use of a background contraction necessitates that the PSTH reflects not only the corticofugal volley but also transmission through spinal circuitry that is appropriate to the contraction and is conditioned by contraction-associated afferent feedback.

Secondly, the stimulus montage used by Day *et al.* (1989) (cathode over the hand area, anode at the vertex, and vice versa) was not selective for the upper limb though it is, in our experience, the best montage for producing I waves (*see* Figs 1, 5). In these experiments, cathodal stimulation of the hand area would have been associated with anodal stimulation of the leg area. It is likely that there are corticospinal projections from the leg area to upper-limb spinal segments (much as there appear to be projections from upper-limb cortex to lower-limb spinal segments, *see* next section). The biological purpose of such projections could be to bring about appropriate postural adjustments when a limb is moved. If these 'postural' inputs to motor neurons were mediated through interneurons, late peaks of motor neuron discharge might occur in PSTHs.

Lower-limb projection from upper-limb motor cortex

There are a number of possible explanations for the D wave in the low-thoracic recording in response to weak stimulation over the upper-limb area. It is possible that the lower-limb area was inadvertently stimulated, but this is unlikely given the very low threshold for the volley. It is possible that the lower-limb projection was activated deep to the cortex, but again the low threshold makes this unlikely, and there was no evidence of subcortical activation in the high-thoracic recording at these low stimulus levels. The most parsimonious explanation is that there is a direct corticospinal input to lower-limb spinal segments from the upper-limb cortex, as has long been suggested for non-human primates (Sherrington, 1889; Leyton and Sherrington, 1917; Glees and Cole, 1950). Indeed, in cat and monkey, collaterals of corticospinal axons innervating forelimb segments have been demonstrated to project to thoracic and lumbar segments (Shinoda *et al.*, 1976, 1979; *see also* Phillips and Porter, 1977), presumably so that appropriate postural adjustments can be made in the trunk and hindlimbs when the forelimbs are moved. The function of such a projection in human subjects warrants further study, in particular to define whether it is directed to truncal or limb segments and to motor neurons or interneurons, and to determine the sign of any segmental effect.

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SEIZURES INVOLVING SECONDARY SENSORY AND RELATED AREAS

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SUMMARY

Five patients with seizures involving the secondary sensory and/or related areas (SSRA) are presented. Four of five experienced ictal numbness and/or tingling bilaterally and/or axially; this involved fingertips (three patients), lips (two), tongue (two), and was diffuse in one. The fifth patient experienced bilateral ictal pain. Associated ictal symptoms implicating adjacent regions appeared in all five patients, including contralateral clonic movements (two patients), hypersalivation (two), taste (one), vocalization (two), dysphagia (one), and contralateral sensory march (one). Two patients had ictal symptoms suggestive of adjacent temporal lobe involvement. By history, the SSRA was involved at seizure onset in four and by spread in one. All five patients had electroencephalogram (EEG) or subdural EEG supportive evidence of SSRA involvement: ictal (three) and interictal (three). Three patients had lesions in this area shown by magnetic resonance imaging or computerized tomography and all three had histologically proven glial tumours. Relevant experimental physiological and anatomical data are reviewed.

INTRODUCTION

While mapping the sensory area of the cat cortex by potentials evoked from peripheral stimulation, Adrian (1940) discovered a second area representing sensation of the limbs behind the head area of the primary sensory cortex. Subsequent anatomical and physiological studies (Robinson and Burton, 1980*a,b,c*) have revealed several contiguous sensory areas in the lateral sulcus (Sylvian fissure) of cynomolgus monkeys, closely allied in function and structure. Such zones include the secondary sensory area (SII), area 7b of the parietal lobe, the retroinsular (Ri) and posterior auditory (PA) areas, and the granular portion of the insula (Ig) (Robinson and Burton, 1980*b,c*). These areas together are termed 'secondary sensory and related areas' (SSRA) in this paper. In contradistinction to the primary sensory area, peripheral receptive fields of SSRA are less discrete and often bilateral.

From stimulation studies of awake humans at epilepsy surgery, Penfield and Jasper (1954) outlined the SII on the superior bank of the Sylvian fissure of each hemisphere, occupying part of the frontal and parietal opercula. Stimulation produced bilateral, contralateral and even ipsilateral numbness and tingling, particularly of the lips and fingertips. They described two patients whose seizures appeared to engage the SSRA from temporal lobe origins. Single case reports of seizures involving this region have followed (Lesser *et al.*, 1983; Young *et al.*, 1986).

This report of a series of patients with well-documented seizures involving the SSRA is presented to heighten clinicians' awareness of this likely under-recognized seizure disorder.

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METHOD

University Hospital and Victoria Hospital Epilepsy Unit files formed the patient population and provided clinical and laboratory data.

Files were searched for all patients with partial seizures having electrophysiological and/or neuroimaging evidence of an epileptogenic lesion in the left or right frontal-parietal operculum. Three of eight such patients had purely motor phenomena and were therefore excluded. Ictal sensory symptoms were sought specifically in each of these three patients and were not found. The other five patients all had simple partial seizures with prominent sensory phenomena.

Ictal and interictal electroencephalogram (EEG) scalp data were obtained in the usual manner: collodion-applied scalp EEGs according to the International Ten-Twenty System supplemented by mandibular notch electrodes. Bipolar and referential montages were employed. Subdural strip electrodes with 1 cm inter-electrode spacing were inserted in one patient (patient 1) whose scalp EEG data were ambiguous.

RESULTS AND CASE REPORTS

Table 1 outlines clinical and laboratory features of these patients.

Case 1

A 19-yr-old, right-handed lady had a 6-yr history of seizures. Her simple partial seizures consisted of numbness and bilateral tingling of her lips, fingertips and less commonly diffusely throughout her body or throughout her head. Complex partial seizures occasionally issued from simple partial seizures. Consciousness would then be lost associated with staring fearfully, uttering a moan or brief sentences, grinding her teeth, profuse salivation, automatisms with hands, variable unlateralized limb posturing, writhing and hyperventilation. She would occasionally emerge with a motor speech difficulty but not dysphasia. Olfactory, gustatory, abdominal, auditory, *déjà vu* and visual phenomena never occurred. No facial or arm myoclonus was ever observed.

Electroencephalograms showed no spikes or focal abnormality either ictally or interictally. Because of such ambiguous ictal and interictal scalp recordings, subdural strips were placed bilaterally over the temporal, orbital frontal and Rolandic areas. Recordings revealed that typical seizures began in the right frontal-parietal operculum associated with tingling in the hands, lips and a feeling of fear. These rarely spread to the right temporal convexity, but never appeared in right inferior temporal electrodes (Fig. 1). A magnetic resonance imaging (MRI) scan was normal. Partial resection of the right frontal-parietal operculum has abolished her seizures for 6 mths. No specific abnormality appeared on the resected specimen.

Comment. These seizures probably originated in the SSRA (axial and bilateral sensations) and spread to the limbic part of the temporal lobe (staring fearfully, automatisms) and to the superior bank of the Sylvian fissure (salivation). Vocalization may indicate lower primary motor involvement. Whether the writhing and posturing represent distant propagation to the supplementary motor region (Penfield and Jasper, 1954) or automatisms of a complex partial seizure is unproven here.

Case 2

A 68-yr-old, right-handed man with no previous neurological history had 30 s episodes beginning with a sour taste followed by a rising abdominal sensation, euphoria, fear, a sensation of leaving his body and occasionally diffuse bilateral tingling of the tongue.

TABLE 1 CLINICAL DATA

Present age	*Age seizure onset*	*SSRA** ictal symptoms*	*Extra SSRA ictal symptoms*	*EEG and subdural EEG data*	*Aetiology*
19 yrs	13 yrs	*(i) Numbness of lips, fingertips, occasionally diffusely	(i) Follow SSRA symptoms: loss of consciousness, fearful stare, moan or brief sentences, grinding teeth, automatisms, salivation, limb posturing, writhing, hyperventilation	Subdural-recorded SSRA seizure (Fig 1) Interictal spikes at SSRA	Unknown. MRI, microscopy normal
70 yrs	68 yrs	(i) Diffuse tingling of tongue (ii) Warm sensation back of neck; and bilateral tingling of fingers	(i) Sour taste → rising abdominal sensation → euphoria → sensation of leaving his body → fear	EEG right temporal-frontal-central spikes	Unknown. MRI, CT normal
58 yrs	52 yrs	(i) Diffuse perioral and tongue numbness	(i) Dysphagia and sensation of pharyngeal constriction → guttural sound → right mouth, face myoclonus	EEGs: left fronto-central seizures	MRI: tumour left frontal-parietal operculum-superior bank of Sylvian fissure
48 yrs	46 yrs	(i) Simultaneous right foot, hand, face, mouth numbness without march → right arm feels outside of body (ii) Bilateral numbness of fingertips	(i) Excess salivation	EEG· bitemporal delta and spikes, principally left	MRI left insula tumour
64 yrs	64 yrs	(i) Right cephalic sensation → sharp pain in arms and upper trunk → lower trunk, legs	(i) Right sensory march (head, face, throat) → right face myoclonus	EEG: recorded seizure left parietal, central, posterior mid-temporal	CT: left posterior temporal malignant astrocytoma

* Each number = one seizure type; ** includes SII and adjacent cortical regions (*see* comments and Discussion).

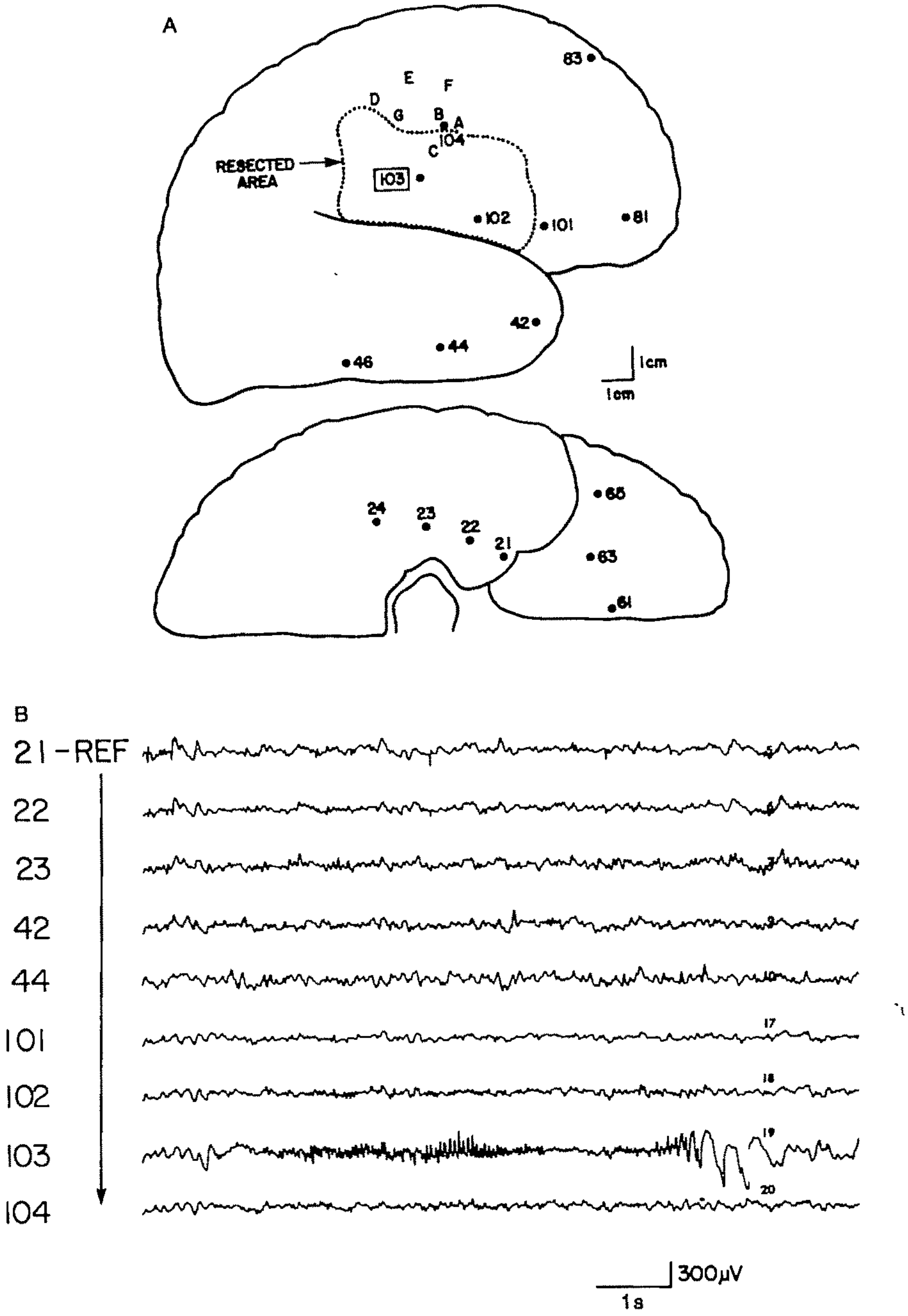

FIG. 1. A, numbers = location of subdural electrode positions recorded in B. Letters = sites of electrical stimulation eliciting responses: A = contralateral eye opening and arching of the eyebrow, B = repetitive flexion of index finger; C = eye and mouth movement and extension of neck; D = tingling of tongue diffusely; E = extension of the ring and small finger; F = apposition of the thumb to the fingers, G = extension of the fingers and abduction of the thumb. Finger, eye, mouth movements all contralateral (*left*). C is the only site within the circle from which symptoms were elicited. B, tingling of hands, lips with sequential polyspikes at 103 without spread.

Bilateral tingling of his fingers associated with a warm sensation of his neck posteriorly occasionally followed the taste. Neurological examination was normal. An EEG showed frequent right anterior mid-temporal spikes with considerable supra-Sylvian spread to the frontal and central regions and sporadic spread to the parietal-posterior temporal areas. An MRI and a computerized tomography (CT) scan were normal.

Comment. These attacks may have begun in the superior bank of the circular sulcus adjacent to the insula (taste) (Penfield and Jasper, 1954) or the parietal operculum (Hausser-Hauw and Bancaud, 1987) and spread to involve the limbic part of the temporal lobe and/or insula (abdominal sensation, fear) and to the secondary sensory area (tingling of tongue, fingers).

Case 3

A 58-yr-old, thoroughly left-handed, registered nurse had a 6-yr history of seizures beginning with peri-oral and diffuse tongue numbness associated with an inability to swallow. In association with a sensation of pharyngeal constriction, she emitted a guttural sound, then twitching of the right side of her mouth and face occurred without spread. Post-ictally an accentuation of her usual slight word-finding difficulty occurred for about 2 min. On examination her right nasal labial fold was decreased, but the motor system was otherwise normal. Electroencephalograms recorded electrographic seizures over the left frontal-central regions. An MRI scan showed a mass in the left lower Rolandic area extending to the superior bank of the Sylvan fissure (Fig. 2) which on pathological examination of a partially resected specimen was an oligodendroglioma.

Comment. The peri-oral and diffuse tongue numbness indicated a seizure origin in the SSRA with spread to the lower primary motor region (pharyngeal constriction, vocalization, right facial twitching).

Case 4

A 48-yr-old, right-handed woman presented with a 2-yr history of episodes commencing with sudden numbness and tingling occurring simultaneously in her right face, mouth, hand and foot without a sensory march. These were followed by a feeling that her right arm was outside of her body and by a loss of confidence in its performance. She was surprised that it functioned normally. Then bilateral numbness of her fingertips and excessive salivation occurred. Neurological examination was normal. Electroencephalograms showed bitemporal delta, more persistent on the left and independent left and right anterior-inferior mid-temporal spikes, more common on the left. The MRI showed a well-defined left insula lesion involving the external capsule and posterior aspect of the internal capsule as well as extension into the temporal stem with areas of haemorrhage and cyst formation within it. This location was confirmed at surgery; partial resection of the tumour disclosed an anaplastic oligodendroglioma.

Comment. Her seizures probably originated in the secondary sensory area (widespread right sensation, bilateral sensation) and possibly in the lower part of the primary sensory area and spread to the superior bank of the Sylvian fissure (salivation) (Penfield and Jasper, 1954).

Case 5

The 8-mth history of this 64-yr-old man was reported previously (Young *et al.*, 1986). His attacks began with a right cephalic sensation that moved to his right face and then

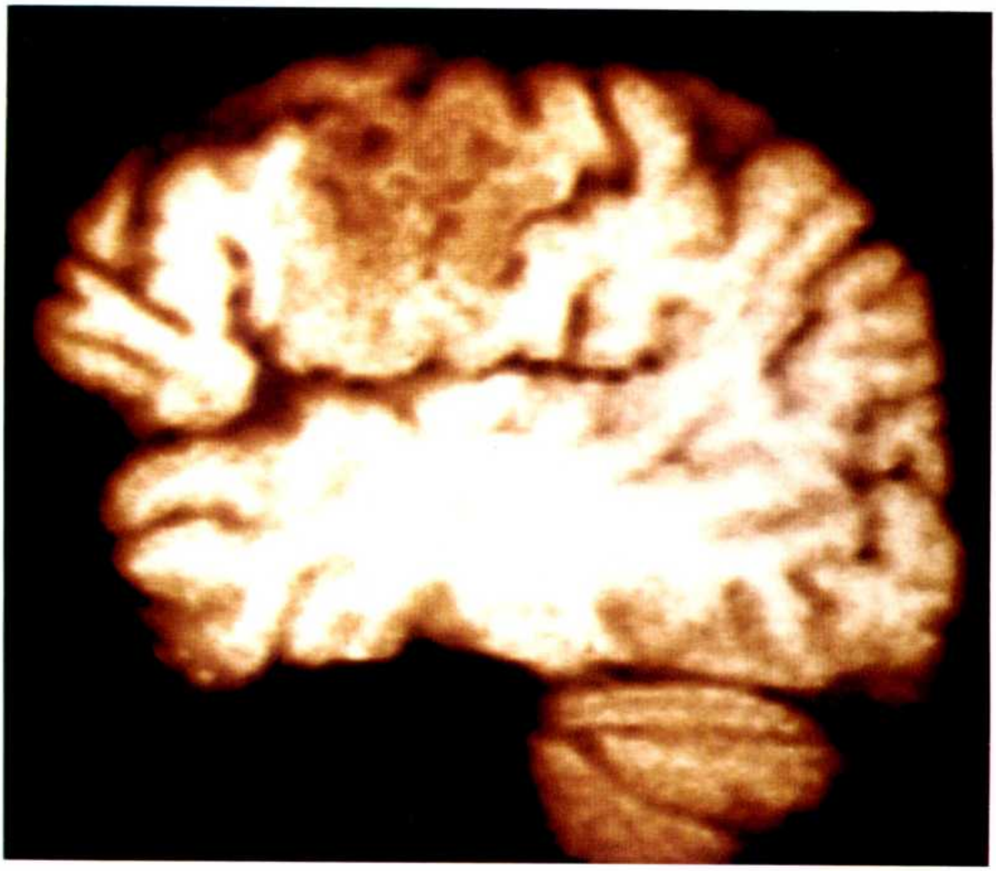

FIG. 2. Image-enhanced sagittal MRI of left hemisphere of patient 3 illustrating diffuse Rolandic tumour extending to Sylvian fissure. Expanding pixel values to fill entire pixel range enhanced original MRI. Colour brightness varies directly with MRI density.

to the throat followed by right face twitching. Two days prior to referral frequent painful seizures began with the same right cephalic sensation followed by sharp pain in both arms and upper trunk which descended in 'waves' down the trunk into his legs. Neurological examination was normal. An EEG-recorded seizure began with 25 Hz waves in the left parietal region that evolved to 4 Hz waves over the left central parietal and mid-posterior temporal region associated with his typical right-sided sensory motor attacks. A CT scan showed a hypodense lesion in the posterior superior aspect of the left temporal lobe which enhanced with contrast; biopsy revealed a malignant astrocytoma.

Comment. His right cephalic, face and throat sensations may reflect secondary sensory involvement and possibly adjacent primary somatosensory region while the subsequent motor symptoms indicate spread to the lower part of the precentral gyrus. Pain may represent involvement of area 7b of the parietal operculum or the insula (Robinson and Burton, 1980*a*,*b*).

Summary of symptoms and supporting data

Thus four or five patients experienced ictal numbness and/or tingling bilaterally; this involved the fingertips (three patients), lips (two) and tongue (two), and was diffuse in one. Two patients had contralateral widespread numbness. One patient had bilateral pain beginning in the arms and descending the trunk to involve the legs. In addition to SSRA involvement, all five patients had at least one associated symptom suggesting engagement of a contiguous structure(s) including: the peri-insular region (three patients), the temporal lobe (two patients), the lower primary sensory cortex (two patients) and motor cortex (three patients). Supporting laboratory data included ictal EEG/subdural EEG (three patients), interictal EEG/subdural EEG (three patients) and neuroimaging (three patients).

DISCUSSION

Several contiguous zones of the frontal-parietal operculum including the superior bank of the Sylvian fissure receive somatosensory afferents correlating with the prominent sensory symptoms of seizures involving this region. Such zones include the SII, area 7b of the parietal lobe, the Ri and PA areas and the Ig (Robinson and Burton, 1980*b*,*c*). Early studies (Adrian, 1940; Woolsey and Bard, 1943; Woolsey, 1944; Woolsey and Fairman, 1946) only recognized SII as occupying this role.

Early studies

Adrian (1940) first discovered SII in the ectosylvian gyrus of cats posterior to the head region of the primary sensory cortex (SI). This area responded to cutaneous tactile and pressure stimulation in a manner dissimilar to SI: under light anaesthesia, stimulation of either an ipsilateral or contralateral limb would evoke a widespread surface cortical response. Within SII, Adrian found the forefeet to be represented anteriorly and the hindfeet posteriorly with the distal limbs represented over a larger area than the proximal regions.

Subsequent works confirmed Adrian's finding that contralateral and ipsilateral cutaneous stimuli each evoked responses in this region recorded either on the cortical surface of all mammals examined (Woolsey and Bard, 1943; Woolsey, 1944; Woolsey and Fairman, 1946) or as single units with microelectrodes (Carreras and Andersson, 1963).

Contralateral and bilateral receptive fields

Level of anaesthesia has strongly affected experimental results. Under deep anaesthesia only responses from the contralateral side have been evoked, whereas contralateral responses were twice as large as ipsilateral ones in light anaesthesia (Woolsey and Bard, 1943; Woolsey, 1944; Woolsey and Fairman, 1946; Carreras and Andersson, 1963). Whitsel *et al.* (1969), recording with microelectrodes in unanaesthetized cats and monkeys, obtained responses in most secondary sensory area neurons to cutaneous stimulation of either side.

From microelectrode recording of responses to light mechanical stimulation, Robinson and Burton (1980*a*) found 68% of neurons to have mainly contralateral receptive fields (RFs), 26% bilateral and 6% ipsilateral (their Table I). Contralateral RFs were more common in the hands and digits while only the SII trigeminal distribution had predominantly bilateral fields. In contrast, SI neurons were only rarely activated by ipsilateral stimulation (Carreras and Andersson, 1963).

Bilateral fields found by these and earlier authors (Adrian, 1940; Woolsey and Bard, 1943; Woolsey and Fairman, 1946; Whitsel *et al.*, 1969) may partially or totally reflect SII afferents from both the ipsilateral and contralateral primary SI (Jones and Powell, 1970; Burton and Jones, 1976). The SII receives commissural afferents from both SI and SII and these are most dense in the face area (Robinson and Burton, 1980*a*; Whitsel *et al.*, 1969; Friedman *et al.*, 1980). The major afferent supply from SI may underly the longer evoked response latency in SII as compared with SI (Woolsey, 1944; Woolsey and Fairman, 1946) while the more indirect pathway for ipsilateral response within SII likely explains its longer response latency than that from contralateral stimulation (Woolsey and Fairman, 1946).

Somatotopic organization

Stimuli from the mouth and limb apices evoked the largest potentials over SII (Woolsey and Bard, 1943; Woolsey and Fairman, 1946). Similarly, Whitsel *et al.* (1969) and Robinson and Burton (1980*a*) found that many SII neurons represented the hands and face and these had small, bilateral RFs; fewer neurons represented the proximal limbs and chest and these had large RFs. This explains the frequent sensory symptoms in fingertips, lips and tongue in our patients.

Both SI and SII are somatotopically organized, and the sequence of body representation in SII closely resembles that of SI. From single unit recordings in awake monkeys Robinson and Burton (1980*a*,*b*) found that different body regions are represented cranially to caudally in successive strips across the parietal operculum with an anterolateral to posteriomedial slant as viewed on an unfolded lateral sulcus (Fig. 3). They found neurons with trigeminal RFs to occupy the most anterior portion of SII followed by digits and hands (largest component of map), then arm, trunk and leg. [This sequence closely resembles that obtained earlier by evoked responses to cutaneous stimulation of the lightly anaesthetized dog (Hamuy *et al.*, 1956).] Receptive fields of SII were generally larger than SI. Only the digit regions contained sequentially organized RFs such that the field gradually shifted along the cortex. Organization of the remainder of SII was more complex: at each cortical point each body part would have varying degrees of predominance. Thus neural activity, such as a seizure, passing across this map would be felt as shifting sensations of large areas with indistinct localization and without a well-defined sequence or 'march'. The exception would be a seizure in the areal representation of the digits.

Other opercular sensory areas

These anatomical and physiological properties of SII are reflected in the bilateral and/or diffusely contralateral somatosensory symptoms seen in our cases with seizures arising from this region. However, involvement of other, contiguous sensory areas may also account for bilateral symptoms. Review of these areas follows.

Caudal to SII lies area 7b (Fig. 3). Its connections for somatic stimuli more likely involve thalamocortical afferents (pulvinar, lateralis posterior) than afferents from area 5 (Robinson and Burton, 1980*b*). With single unit recordings of unanaesthetized monkeys

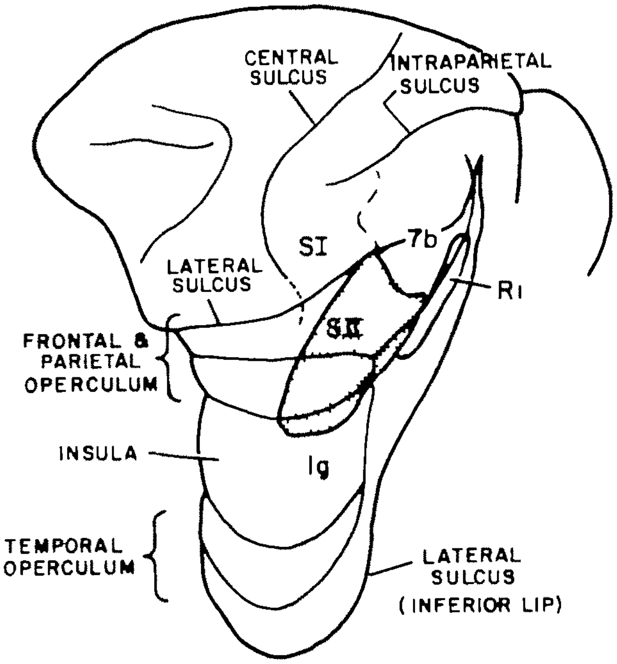

FIG. 3 Orthographic expansion of lateral sulcus cynomolgus cortex showing portions of somatosensory area (SII), primary somatosensory area (SI), area 7b, the retroinsular field (Ri), and the granular insular field (Ig). The post-auditory area (not shown) lies immediately lateral to the Ri area and just posterior to the primary auditory cortex From Robinson and Burton (1980*b*) with permission

Robinson and Burton found that the majority of its neurons responded to ipsilateral as well as contralateral somatic stimuli and its bilateral RFs were occasionally stocking-like. Two features further distinguished 7b from SII: (i) some 7b neurons responded to noxious stimuli as well as innocuous tactile stimulation; (ii) only a crude somatotopic organization existed (Robinson and Burton, 1980*b*,*c*).

Most of the neurons in the Ri, Ig and post-auditory (PA) cortical fields respond to innocuous somatic stimulation. Robinson and Burton (1980*b*) found that more Ri neurons responded primarily to contralateral stimuli than equally to contralateral and ipsilateral input, but in PA the same number of neurons had bilateral as had contralateral fields. As in 7b, no consistent topography could be determined for Ri and PA regions although some cranial-to-caudal body representation was apparent in an anterior-posterior orientation. Ig had no apparent topographical organization.

Thus ill-localized somatosensory phenomena may represent ictal discharge in areas 7b, Ri, PA or Ig as well as SII. Bilateral sensory phenomena could arise from any of these areas, particularly SII, 7b and PA.

Bilateral face and buccal sensation may result from discharge in the trigeminal area of SII which has the highest percentage of SII neurons responding to both ipsilateral and contralateral stimulation (Robinson and Burton, 1980*a*). An additional mechanism may be discharges involving both the contralateral SI face area and the anteriorly adjacent ipsilateral face area described in monkeys and other mammals by Woolsey and Fairman (1946).

Human studies

In 16 human patients with various seizure disorders stimulated at surgery, Penfield *et al.* (Penfield and Rasmussen, 1950; Penfield and Jasper, 1954) found Adrian's and Woolsey's 'secondary sensory area' to occupy the frontal and parietal opercula including 'the superior border and superior bank of the fissure of Sylvius of both hemispheres'. Cortical electrical stimulation of this region at surgery produced widespread numb, tingling and/or prickling sensations bilaterally but maximally contralaterally. Such sensations were occasionally confined to the tongue and fingers. These results corresponded closely to experimental data (above) and to the ictal symptomatology of our patients. Symptoms obtained by Penfield referrable to motor control are less easily interpreted: a desire to move a contralateral limb or a feeling of its awkwardness or weakness. One of our patients (patient 4) doubted that her contralateral right arm would function normally and was surprised that it did.

The discharges of the two patients with secondary sensory seizures cited by Penfield and Jasper (1954) appeared to have spread ictally from the adjacent temporal lobe: B. McK., with traumatic atrophy of the right anterior temporal lobe had attacks of an abdominal sensation followed by a sensation of her mouth and hands bilaterally; A. Bo., with a right temporal glioma, had episodes of macropsia, bitter taste then diffuse left-sided tingling. The seizures of our patient 2 probably spread to the SSRA from adjacent regions. (*See* comments in Results.)

Burton and Jones (1976) found increased regional cerebral blood flow by positron emission tomography in SI and a second focus in the parietal operculum in association with vibratory stimulation of contralateral fingers. This second focus corresponds to second somatic sensory cortex (SII).

Tumour is the most common known aetiology in our series (three of five cases) and in the literature (two of three cases) (Penfield and Jasper, 1954; Lesser *et al.*, 1983).

In addition to ictal symptoms, laboratory data supported secondary sensory involvement in all five of our cases: scalp or subdural recorded seizures (three cases), focal interictal spikes (three cases) and neuroimaging (three cases). Which of the experimentally defined cortical areas in the frontal-parietal operculum is/are involved in each instance cannot be determined from clinical data. Indeed experimentally, distinctions among cortical areas could only be made by studying behavioural properties of neuronal aggregates, cytoarchitecture and anterograde and retrograde tracers (Friedman *et al.*, 1980; Robinson and Burton, 1980*a,b,c*). These authors found very gradual transitions among these several cortical RFs.

Of eight patients with evidence of a frontoparietal operculum epileptogenic lesion, five had prominent ictal sensory symptoms described in this paper. Diffuse or bilateral sensory phenomena without a discrete 'march' involving large somatic areas, limb apices or axial structures may also represent seizures in the amygdala (Gloor, 1972) or supplementary sensory area (Penfield and Jasper, 1954) as well as SII and related areas (SSRA). Such sensory symptoms may represent epileptic discharge confined to the SSRA or may reflect coincident involvement of the SSRA and a structure of propagation, such as the amygdala. Co-activation of originating and propagated structures has been postulated for ictal experimental phenomena by Gloor (1990) and Blume *et al.* (1992).

Thus, seizure involvement of the SSRA should be considered when ictal symptoms include bilateral paraesthesiae, dysaesthesiae or pain, either of the face, distal extremities or diffusely. Such involvement should be particularly suspected when evidence of ictal involvement of contiguous structures is present such as hypersalivation (peri-insular region) or unilateral facial or buccal myoclonus (inferior primary motor region). As the frontal-parietal operculum is the only cortical area known to produce these ictal symptoms (Penfield and Jasper, 1954), they most likely represent contiguous spread and not distant propagation.

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MORPHOMETRY OF THE SYLVIAN FISSURE AND THE CORPUS CALLOSUM, WITH EMPHASIS ON SEX DIFFERENCES

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SUMMARY

The relationship between anatomical asymmetries in the perisylvian region and the sizes of different regions of the corpus callosum was investigated post-mortem in 40 brains of right-handed hospital admissions (20 males, 20 females) with no cortical involvement. There were no sex differences either in anatomical asymmetries or in regional size of the callosum. There was a negative correlation between the absolute value of Sylvian fissure (planum temporale) asymmetries and the size of the isthmus in males but not in females. Further, there was a significant negative correlation between the size of the Sylvian fissure (or planum temporale) and the size of the callosal mid-body in males but not in females. There was no correlation between the asymmetry of the planum temporale |left−right| and total size of the planum (left+right). These findings constrain theories about the ontogenesis of hemispheric specialization through changes in callosal connectivity and about sex differences in interhemispheric organization.

INTRODUCTION

It has been established for some time that in the human brain, anatomical asymmetries exist in regions related to Wernicke's area, specifically the Sylvian fissure and the planum temporale (Geschwind and Levitsky, 1968; Galaburda *et al.*, 1978). Furthermore, some evidence suggests that a correlation exists between the direction and degree of functional lateralization and the anatomical asymmetries seen in these regions (Ratcliff *et al.*, 1980; Strauss *et al.*, 1985; Witelson and Kigar, 1988).

However, there is controversy about more detailed aspects of these anatomical bases of functional lateralization. First, the developmental mechanisms producing asymmetries are still unclear. Secondly, the contribution of callosal connectivity to individual differences in functional lateralization is yet to be comprehensively analysed (Witelson, 1985, 1989; Kertesz *et al.*, 1987; Zaidel *et al.*, 1990). Weaker functional lateralization could be due to several factors, one of which is hemispheric specialization, perhaps indexed by anatomical asymmetry, and another is callosal connectivity, perhaps indexed by callosal size. Thirdly, conflicting reports have arisen regarding sex differences in commissural connections (de Lacoste-Utamsing and Holloway, 1982; Clarke *et al.*, 1989; Witelson, 1989; Allen *et al.*, 1991) and in functional lateralization (Bryden, 1982; Geschwind and Galaburda, 1985; Galaburda *et al.*, 1990; Voyer and Bryden, 1990). The present paper is an attempt to clarify some of these questions from an anatomical perspective.

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Only a few studies have been concerned with the developmental morphometry of perisylvian asymmetries in humans. One of these suggests that such asymmetries are produced by left-right differences in the timing of hemispheric growth and maturation (Chi *et al.*, 1977). More recently, Geschwind and Behan (1982) and Geschwind and Galaburda (1985) proposed that in foetal life testosterone activity could affect unequally the growth of the two hemispheres, leading to deviations from the normal asymmetric pattern.

Galaburda *et al.* (1987) further argued that if testosterone activity slowed down the development of the (usually larger) left hemisphere language regions [as Geschwind and Behan (1982) originally proposed] this would produce a compensatory greater growth of the (usually smaller) right regions, leading to more symmetric brains. However, in more recent articles (Galaburda *et al.*, 1990; Rosen *et al.*, 1990), Galaburda *et al.* have proposed that early in ontogeny the brain is relatively symmetric, and the loss of cells in the prospective smaller hemisphere leads to an asymmetric pattern. In any case, they propose that the size of the smaller side (the right one in leftward asymmetric brains and the left one in rightward asymmetric brains) determines the extent of asymmetries in the Sylvian region. This proposal was based on their observations (Galaburda *et al.*, 1987) that asymmetry coefficients in the human planum temporale correlated with the size of the right planum but not the left in leftward asymmetric brains, and with the size of the left planum but not the right in rightward asymmetric brains.

Rosen *et al.* (1989, 1990) and Galaburda *et al.* (1990) have also proposed that an inverse relationship may exist between the magnitude of anatomical asymmetries (regardless of direction) and the degree of commissural connectivity in the respective cortical regions. This suggestion is based on the negative correlations seen between the density and relative extent of callosal terminations and volumetric asymmetries in the somatomotor cortex of the rat (Rosen *et al.*, 1987, 1989, 1990). Further support for this concept comes from Witelson's (1985, 1989) findings that left-handers and non-consistent right-handers (presumably representing a less lateralized population than consistent right-handers) tend to have larger corpus callosums than consistent right-handers. This finding has been challenged by Kertesz *et al.* (1987), who did not find a correlation between handedness and callosal size. However, the two groups used different methods to determine handedness (Witelson, 1989). Also, the material used in the two studies was different: Kertesz *et al.* used magnetic resonance imaging (MRI) of the corpus callosum, while Witelson used post-mortem material. Using MRI in graduate students, Clarke (1990) concluded that larger corpus callosums are not associated with greater functional hemispheric symmetry nor with greater hemispheric transfer, but may be related to interhemispheric inhibitory influences (*see* Zaidel *et al.*, 1990).

Another individual difference that is said to affect functional and anatomical asymmetries is gender. There are conflicting reports, some suggesting a higher degree of anatomical asymmetries in females (Geschwind and Galaburda, 1985), and others proposing a higher degree of anatomical and functional lateralization in males (Wada *et al.*, 1975; McGlone, 1980; Bryden, 1982; Kertesz *et al.*, 1987). The consensus may be that there are no consistent sex differences in functional lateralization but perhaps strategy differences which can result in complementary patterns of lateralization in males and females (Kimura and Harshman, 1984; Voyer and Bryden, 1990; Zaidel *et al.*, 1992).

Few studies have parcelled out the relative contributions of hemispheric specialization and of callosal connectivity to sex differences in functional lateralization (but *see* Zaidel *et al.*, 1990). There is some evidence that may suggest that females perform better than males in tasks requiring interhemispheric transfer (Potter and Graves, 1988), although these results may be regarded as preliminary and perhaps methodologically questionable. In addition, there is controversy as to whether there are (de Lacoste-Utamsing and Holloway, 1982; Holloway and de Lacoste, 1986; Clarke *et al.*, 1989; Witelson, 1989; Clarke, 1990; Allen *et al.*, 1991) or are not (Bell and Variend, 1985; Weber and Weis, 1986; Kertesz *et al.*, 1987; Weis *et al.*, 1989) any sexual dimorphisms in the gross structure of the corpus callosum in humans.

In the light of these controversies we undertook a series of morphometric measurements in order to re-examine the anatomical asymmetries in the posterior language areas. In addition, we investigated the anatomical relationship between the degree of asymmetries in the Sylvian fissure and the planum temporale, and the sizes of different portions of the corpus callosum. This approach may provide an insight to the study of the relationship between brain lateralization and interhemispheric communication. Lastly, we searched for the possible existence of sex differences in anatomical asymmetries, callosal size and the relationship between these two. The results may shed light on the issues of gender differences in functional brain lateralization and interhemispheric transfer.

Specifically, our goals were: (i) to analyse the mechanisms generating anatomical asymmetries in humans from a morphometric perspective, in a similar manner to Galaburda *et al.* (1987), and (ii) to test whether there is an anatomical relationship between asymmetries in the perisylvian regions and commissural connections (indexed by callosal size) in humans, as may be deduced from the findings of Rosen *et al.* (1989) in the rat, where an inverse relationship between commissural connections and cortical asymmetries was found. Witelson's (1985, 1989) reports of larger callosums in left-handers also support this concept. This, then, is the first attempt to determine an anatomical relationship between brain asymmetries and commissural connectivity in humans. In addition (iii), we wanted to know whether any sex differences appeared in the extent of asymmetries, in callosal connectivity or in the relationship between anatomical asymmetries and commissural connections.

MATERIALS AND METHODS

Collection of material

Brains were obtained from the Institute of Pathology, Hospital San Juan de Dios, University of Chile, Santiago, Chile. Forty brains (20 females; 20 males), aged 25–68 yrs, of individuals who died from non-neurological disease were examined. No more than 12 h after death, brains were extracted from the skull and immersed in 20% buffered formalin for 7 d. After this, brains were visually inspected on the surface for gross morphological abnormalities. Distortion of the shapes of the brains was avoided by suspending them from the basilar artery.

Pictures of the brains

After 7 d, brains were sectioned at the level of the brainstem and cerebellum. After this, brains were sectioned sagittally in the mid-line, each hemisphere was weighed, and the lateral and medial surfaces were photographed (*see* Figs 1, 3). In these pictures the medial plane was held perpendicular to the photographic axis.

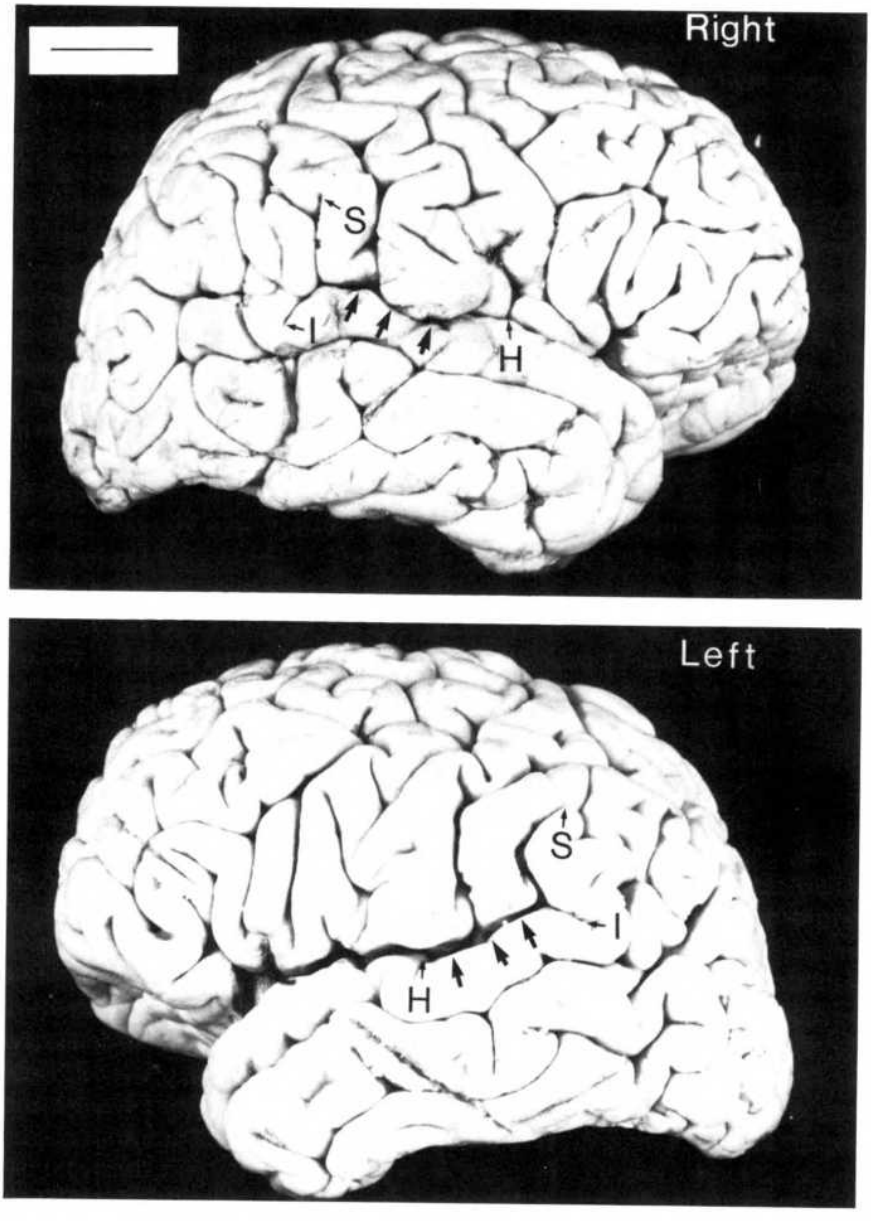

FIG. 1. Lateral views of the cerebral hemispheres. Pictures of this surface were taken perpendicular to the plane formed by the medial surface. The figures show the Sylvian fissure (big arrows), its superior (S) and inferior (I) branches and the location of the posterior border of Heschl's first gyrus (H). The curved distance between H and S was called SF. Bar = 2 cm.

Measurements of the Sylvian fissure and planum temporale

The planum temporale was exposed by the same procedure as described by Geschwind and Levitsky (1968), and pictures were taken from it (Fig. 2). From the pictures of the planum temporale, we determined

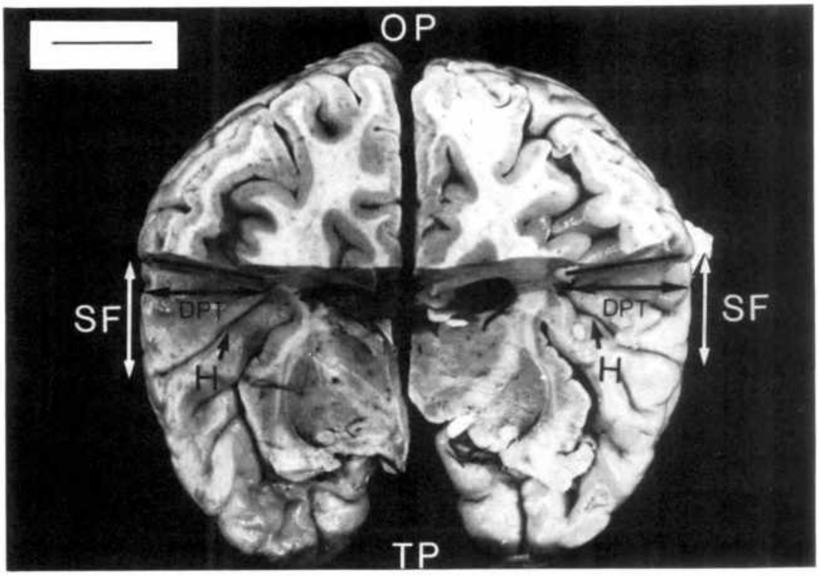

FIG. 2. Exposed surface of the superior temporal lobe. It shows the planum temporale, which is the triangle-shaped structure located between the posterior border of Heschl's first gyrus (H) and the posterior end of the Sylvian fissure (black bar). The distance DPT inside the planum is also shown. SF = Sylvian fissure (posterior and superior aspect); OP = occipital pole; TP = temporal pole. Bar = 2 cm.

where the first gyrus of Heschl was located in the lateral view of the Sylvian fissure (Fig. 1). With this information, it was possible to measure the curved distance between the posterior end of Heschl's first gyrus and the posterior end of the Sylvian fissure in the lateral pictures of the brain (SF in Fig. 2). From the lateral view, the posterior portion of the Sylvian fissure is located in the central area of the hemisphere, so that distortion due to curvature is minimal. The Sylvian fissure usually bifurcates in a superior and an inferior branch at its posterior end. As seen from pictures in published material, it seems that the superior branch has been used for planum temporale measurements (Witelson and Kigar, 1987, 1990; Ono *et al.*, 1990). We measured the superior and the inferior branches of the Sylvian fissure, as well as the distance from Heschl's gyrus to the point of bifurcation (Fig. 1). However, the only measurement that yielded interesting results was the distance from Heschl's first gyrus to the end of the superior branch of the Sylvian fissure (SF in Fig. 2). The other two measurements are consequently omitted from the paper. This issue is further discussed in the Discussion section below.

Curved SF distances (*see* Fig. 2) were calculated both by using a mechanical curvimeter and a computerized digitizing system. The correlation between both measurements was high ($r > 0.9$, $n = 40$). The digitized measurements were used for comparisons.

From the planum temporale pictures, a line perpendicular to the lateral edge of the planum was traced to the medial angle of the planum (formed by the intersection of the posterior sulcus of Heschl's first gyrus and the medial/posterior edge of the planum), and its length measured (Fig. 2). This distance was called the planum temporale depth (DPT).

The planum temporale has a roughly triangular shape as seen from pictures (Fig. 2). The distance DPT corresponds to the height of the triangle, while the length of the Sylvian fissure (SF measurements) corresponds to the base of the triangle. We estimated the area of the planum temporale (PT) by calculating the area of the triangle for each of the SF measurements we used.

Measurements of the corpus callosum

The midsagittal area of the corpus callosum was obtained from pictures of the medial surface of the brain (Fig. 3). The corpus callosum was then parcellated according to straight rostrocaudal length, in a

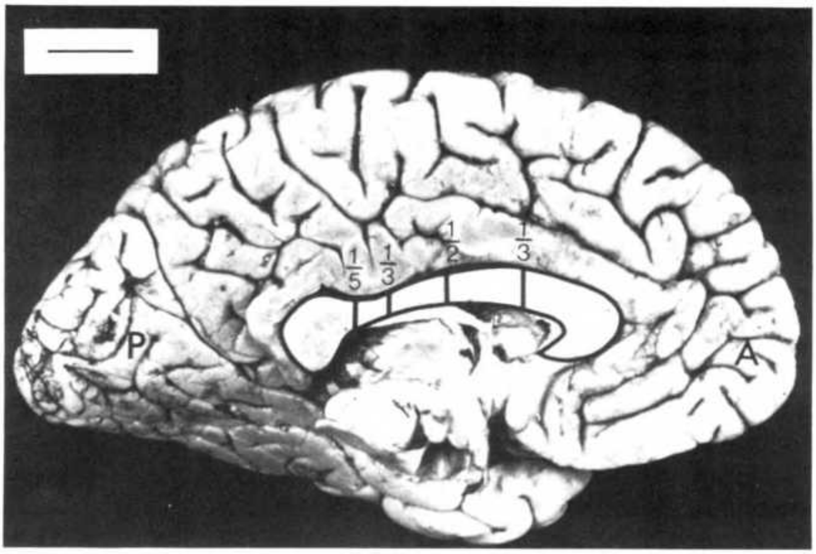

FIG. 3. Partition of the corpus callosum. Total straight length was measured as the maximal length measurable. This measure was divided in half, thirds and fifths. The anterior third is the genu; the area between the anterior third and the midpoint is the anterior mid-body; the area between the midpoint and the posterior third is the posterior mid-body; the area between the posterior third and the posterior fifth is the isthmus; and the area of the posterior fifth is the splenium. A = anterior; P = posterior. Bar = 2 cm.

similar manner as was done by Witelson (1989, 1990). The different callosal portions are: (i) anterior third (genu); (ii) area between anterior third and half the callosal length (anterior mid-body); (iii) area between half the callosal length and posterior third (posterior mid-body); (iv) area between posterior third and posterior fifth (isthmus); (v) posterior fifth (splenium).

Clarke *et al.* (1989) devised a partition of the corpus callosum based on curved length instead of straight length. Recent studies by Clarke (1990) have shown that the results obtained with this method are virtually identical to those obtained with Witelson's (1989, 1990) partitioning methods.

For measuring callosal area, the images of the corpus callosums as seen in pictures of the medial surface of the brains were traced and digitized, and then computerized algorithms were used to partition the corpus callosum. Callosal images from pictures of the left and right hemispheres were traced, and their mean values were used in the study. The correlation between left and right measurements was high ($r > 0.9$, $n = 40$). For comparison, callosal area was also measured by using a computerized planimeter. Correlations between measurements using both techniques were high ($r > 0.9$, $n = 40$).

A linear measurement, minimal callosal width, was measured in the corpus callosum. This was done by drawing a longitudinal line through the centre of the corpus callosum, maintaining an equal distance between the dorsal and ventral borders. The minimal callosal width is the shortest line that can be drawn perpendicular to the central line in the whole callosum. With the exception of six cases in which this distance was found in the posterior body, all callosums had their minimal width located in the isthmus.

Age correlation

The mean age for females was 45.1 yrs (SD = 14.1) and for males was 48.5 yrs (SD = 11.47). There was no significant correlation between age and any of the morphometric measures used, either in the total sample or after separating according to sex.

Morphometry and statistics

The different measurements obtained were normalized for overall size only if a significant correlation existed between the measurements and the size factor. Anatomical asymmetries in the perisylvian region were expressed as the absolute difference between left and right values |left−right|, except for one situation where asymmetries were separated according to whether the larger side was the left or the right, and a case in which an asymmetry index |left−right|/(left+right) was used (both instances are specified in the text). Unless specified, we will use the word 'asymmetry' to denote absolute values (i.e. regardless of direction) of asymmetries instead of real values, which may be either positive (left > right) or negative (left < right).

For all statistical analyses, significance levels of 5% and 1% were pointed out. Since in the present work there are many correlations performed, it is likely that some apparently significant correlations are spurious. However, since this appears as the first attempt to make a morphometric analysis of the language areas together with the corpus callosum, we considered that it was important to outline the trends that could be seen in order to test their validity in the future. All variables passed the standard tests of normality. Comparisons between groups were made using two-way analyses of variance, and Pearson product moment correlations were used for testing the correspondence between variables. Comparisons between correlation coefficients were made using Fisher's r-Z' transformation. All analyses were done with the total sample of 40 subjects, except when separating the two sexes, where n = 20. The number of subjects will be specified only if different from 40.

RESULTS

Measurements of the Sylvian fissure and planum temporale

Means and variances. Table 1 shows the means and standard deviations of the measurements of the Sylvian fissure (SF) and planum temporale depth (DPT). Although the mean in the left side was larger than in the right one in all measurements, the difference was significant only for DPT [F(1,38) = 4.396, $P < 0.05$]. When estimating planum temporale area (PT) from these variables (*see* Materials and methods), we also found a side-effect in favour of the left side [F(1,38) = 4.188, $P < 0.05$].

From Table 1 it can also be seen that most of the variation in the area of the planum

TABLE 1 MEASUREMENTS OF THE SYLVIAN FISSURE· MEANS AND STANDARD DEVIATIONS OF THE BASIC PARAMETERS USED IN THIS STUDY

	SF		*DPT*	
	Mean (mm)	*SD*	*Mean (mm)*	*SD*
Males and females (n = 40)				
Left	46 4	10.8	28.9	2.7
Right	42.9	11.4	27 9	3.3
Left > right	26 subjects		28 subjects	
Left < right	14 subjects		12 subjects	
Females (n = 20)				
Left	44.4	10.9	28.2	2.6
Right	41.3	13 5	26.7	3 7
Left > right	13 subjects		14 subjects	
Left < right	7 subjects		6 subjects	
Males (n = 20)				
Left	48.3	10.5	29.7	2 7
Right	44.5	8.8	29.0	2.4
Left > right	13 subjects		14 subjects	
Left < right	7 subjects		6 subjects	

SF = length of the Sylvian fissure, DPT = depth of the planum temporale.

temporale is located in the longitudinal dimension (SF measurements), rather than the transverse dimension (DPT measurements, *see* Fig. 2). Variation in SF measurements is three to four times as large as variation in DPT. Accordingly, planum temporale area estimations (involving SF and DPT measurements; *see* Materials and methods) correlated much better with SF measurements ($r = 0.93$ and 0.96 for the left and the right sides) than with DPT measurements ($r = 0.42$ and 0.61 for the left and the right sides). Also, when correlating planum area estimations to other variables the results were usually closer to those obtained with SF values than to those obtained with DPT values (*see below*).

Dependency of SF and PT on brain weight. In order to determine whether Sylvian fissure measurements needed to be corrected for brain size, we correlated SF and DPT values with brain weight. The SF measurements did not correlate significantly with brain weight even when the sample was separated according to sex ($r < 0.25$). The DPT distances measured depended on brain size (the left hemisphere: $r = 0.34$, $P < 0.05$, and the sum of left+right: $r = 0.36$, $P < 0.05$), but the correlation lost significance when separating by sex ($r < 0.38$, $P > 0.05$, $n = 20$). When using PT measurements, the results showed a dependency on brain weight similar to DPT (the left side correlated significantly with brain weight: $r = 0.33$, $P < 0.05$, as well as the sum of left+right: $r = 0.34$, $P < 0.05$). These correlations lost significance when sexes were separated. Summarizing, only DPT and PT measurements showed a significant dependency on brain weight in the whole sample ($n = 40$).

Asymmetries and their size dependency. It was also important to know whether asymmetries in perisylvian regions depended on the sum of left plus right measurements. We tested the correlation between the right plus the left perisylvian measurements (SF, DPT, PT) and the absolute value of their asymmetries |left−right|. The results are seen in Table 2. Depth of the planum temporale measurements were the only parameter in which there was a significant (negative) correlation between |left−right| and (left+right). In all these measurements, the left and the right sides were significantly correlated ($r > 0.31$, $P = 0.05$ for SF and PT, and $r = 0.34$, $P < 0.001$ for DPT).

The correlation between |left−right| and (left+right) has an intrinsic tendency to be positive because larger values tend to have larger differences than smaller values. Nonetheless, in the cases of SF and PT we found no significant correlation between |left−right| and (left+right). This may reflect in part the fact that left and right are not independent but rather are positively correlated. The case of DPT, however, may need additional explanation.

Right side versus left side contributions to asymmetries. We intended to test the prediction of Galaburda *et al.* (1987) that perisylvian asymmetries are produced by a

TABLE 2 CORRELATIONS (r VALUES) BETWEEN RIGHT PLUS LEFT PERISYLVIAN MEASUREMENTS AND THE ABSOLUTE VALUE OF THEIR ASYMMETRIES

	SF	*DPT*	*PT*
|Left−right| versus (left+right)	−0.03	−0.40**	−0.05

*Indicates $P < 0.05$; **indicates $P < 0.01$. PT, planum temporale area. Other abbreviations as in Table 1 $n = 40$.

decrease in the prospective smaller side (*see* Introduction). For this, the contribution of the variation in size of either side (left or right) in the production of asymmetries was analysed. The sample was separated into individuals with a larger left side (positive asymmetries) and individuals with a larger right side (negative asymmetries), in the same way as Galaburda *et al.* (1987) proceeded. Then, we correlated the asymmetry values to the sizes of the left and of the right sides in each subsample, again following Galaburda *et al.* (1987).

Table 3 shows the results obtained. In the case of SF and PT values, the size of the right side was apparently more important than the size of the left side in determining the degree of asymmetry. However, the differences in r values were not significant in any of the cases (*see* Table 3). Asymmetries in DPT correlated only with the smaller side in each case (i.e. the right side in positive asymmetries and the left side in negative asymmetries, *see* Table 3), as proposed by Galaburda *et al.* (1987). The differences in r values were significant for leftward but not for rightward asymmetric brains (*see* Table 3).

TABLE 3 CORRELATIONS (r VALUES) BETWEEN THE ASYMMETRIES (LEFT MINUS RIGHT) AND THE SIZE OF EACH OF THE TWO (LEFT AND RIGHT) PERISYLVIAN MEASUREMENTS[1]

	Left side	*Right side*	*n*	*Z'*
SF asymmetries				
Left > right	0 32	−0.41*	26	0 35
Left < right	0.54*	−0.68**	14	0 50
DPT asymmetries				
Left > right	0.06	−0.69**	28	2.79**
Left < right	0 62*	−0.05	12	1.43
PT asymmetries				
Left > right	0.28	−0.44*	23	0.58
Left < right	0 34	−0.65**	17	1.11

[1] For each measure, the sample was separated into those cases where the left side was larger (left > right) and those cases where the left side was smaller (left < right). Z' indicates the differences in r values for each row, expressed as Z values *Indicates $P < 0.05$, **indicates $P < 0.01$ Abbreviations as in previous tables.

The overall pattern differs from that proposed by Galaburda *et al.* (1987), who suggest that the smaller side determines the extent of asymmetries in both leftward and rightward asymmetric brains. However, they used an asymmetry coefficient instead of the raw difference between left and right, and it is not specified which branch of the Sylvian fissure was used in their measurements.

Sex differences in the perisylvian region. No significant sex differences were found in SF measurements, although male measurements were on average slightly larger than female's. Likewise, the proportion of individuals with rightward asymmetries was about the same in both sexes (Table 1). The depth of the planum temporale showed a significant sex difference [F(1,38) = 6.507, $P < 0.02$], in favour of males. Planum area showed a tendency to a sex difference, again in favour of males [F(1,38) = 3.493, $P < 0.07$].

No interaction was found between side and sex for any of these variables [$F(1,38) < 0.7$, $P > 0.4$].

Corpus callosum

Callosal size and its dependency on brain weight. Since most of the relationships found in this section showed a sex bias, sex differences will be analysed in each subsection. The sizes of the different callosal regions in males and in females are shown in Table 4.

TABLE 4 CROSS-SECTIONAL SAGITTAL AREAS OF THE DIFFERENT PORTIONS OF THE CORPUS CALLOSUM (CC) AND THEIR STANDARD DEVIATIONS

			Mid-body			
	Total CC	*Genu*	*Anterior*	*Posterior*	*Isthmus*	*Splenium*
Females and males: area						
Mean (mm^2)	638	277	77	62	56	167
SD	86	43	12	10	13	27
Percentage total						
Mean		43	12	10	9	26
SD		3	1	1	1	3
Females: area						
Mean (mm^2)	616	264	76	62	52	165
SD	81	40	11	10	10	28
Percentage total						
Mean		43	12	10	8	27
SD		2	1	1	1	2
Males: area						
Mean (mm^2)	659	289	78	62	60	170
SD	87	43	13	11	14	26
Percentage total						
Mean		44	12	9	9	26
SD		3	1	1	2	3

The greater overall callosal size of males (about 6% larger), which seems to be concentrated in the anterior callosum (genu), did not reach significance. The isthmus also has a large difference in area between the sexes (13%, larger in males). This difference reached significance [$F(1,38) = 4.67$, $P < 0.05$]. All these differences were minimized and non-significant when brain weight was taken into account. When callosal measurements were corrected for total callosal size, no significant sex differences emerged (Table 4).

A marginally significant correlation ($P < 0.05$) was found between total callosal area and brain weight, which lost significance when sexes were separated (Table 5). In males pooled with females, the genu (anterior third) showed a significant correlation with brain weight ($P < 0.01$) that persisted only in males ($P < 0.05$). When the genu was corrected for total callosal size, the same pattern was found. At the same time, splenial area corrected for total callosal size showed a complementary negative correlation with brain

TABLE 5. CORRELATIONS (r VALUES) BETWEEN CALLOSAL SIZE AND BRAIN WEIGHT IN THE TOTAL SAMPLE, FEMALES AND MALES

	Total CC	*Genu*	*Genu percentage of total*	*Splenium*	*Splenium percentage of total*
Females and males (n = 40)					
Brain weight	0.32*	0.45**	0.44**	0.04	−0.38*
Females (n = 20)					
Brain weight	0.08	0.19	0.33	−0.04	−0 25
Males (n = 20)					
Brain weight	0.31	0.52*	0.49*	0 05	−0.45*

*Indicates $P < 0.05$, **indicates $P < 0.01$. Other callosal regions did not show significant correlations with brain weight. Abbreviations as in previous tables

weight. However, the relationship between un-normalized splenial area and brain weight was non-significant (Table 5).

The area of all callosal segments correlated strongly with total callosal area ($r > 0.7$, $P < 0.01$), and therefore it was appropriate to use normalized measures of callosal segments (*see* Materials and methods).

In summary, no significant sex differences in partial or total callosal size were found, and there was a dependency of callosal size on brain weight which was concentrated in the genu of males.

Dependency of callosal areas on perisylvian asymmetries. To determine a possible link between lateralization and interhemispheric connections, we investigated the relationship between asymmetries in the Sylvian fissure and the size of different callosal regions. When callosal measurements were correlated with the absolute values of SF asymmetries, a significant negative correlation was found between SF asymmetries and isthmus size (real or normalized value) in males only (females: $-0.17 > r > -0.24$, $P > 0.05$; males: $-0.51 > r > -0.53, P < 0.05$, n = 20). The other callosal regions showed a near-zero correlation with SF asymmetries ($-0.1 < r < 0.1$).

The same relationship with isthmus area (real or normalized) was found when using PT estimations, but in this case significance levels rose to $P < 0.01$ (*see* Fig. 4). We also corrected PT values for brain size and found the same results. Additionally, in both SF and PT measurements, we used an asymmetry coefficient defined as |left−right|/(left+right) instead of just the differences between left and right. We found essentially the same results.

The isthmus apparently includes fibres that connect the two perisylvian regions of both hemispheres (de Lacoste *et al.*, 1985; Pandya and Seltzer, 1986). Therefore, this result appears to imply lesser callosal connections between more asymmetric regions, a finding that supports the concept of an inverse relationship between brain lateralization and interhemispheric connectivity (Witelson, 1985, 1989; Galaburda *et al.*, 1990).

Minimal callosal width has been reported as an important parameter in corpus callosum morphometry (Malobabic *et al.*, 1985). Therefore, we also investigated the possible relationship between minimal body width and perisylvian asymmetries. However, we found no significant results.

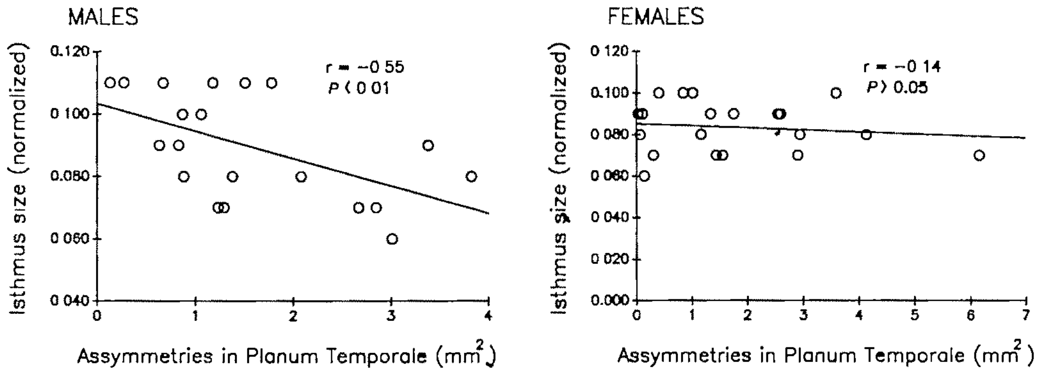

FIG. 4. Plots of absolute values of planum temporale asymmetries against the normalized area of the isthmus of the corpus callosum. Females and males are shown separately The least-squares regression lines are also shown.

Sylvian fissure length and the corpus callosum. When the areas of different callosal segments were plotted against total left+right SF lengths, another interesting relationship emerged. In males only, a negative correlation was found between the anterior mid-body area and left+right SF values ($r = -0.44$, $P < 0.05$, $n = 20$). When the left and the right SF sides were separated, the correlation was significant for the left side only ($r = -0.50$, $P < 0.05$, $n = 20$). In females, these relationships were non-significant ($-0.01 < r < 0.01$).

Corrections for callosal area increased the significance of the correlations in males, but in females there was no significant change (*see* Table 6). When separating right

TABLE 6 r VALUES OF CORRELATIONS BETWEEN THE SIZE OF PERISYLVIAN AREAS AND THE NORMALIZED AREA OF SELECTED CALLOSAL REGIONS

	Females and males (n = 40)	*Females (n = 20)*	*Males (n = 20)*
Anterior mid-body (normalized)			
Left SF	−0.40**	−0.03	−0.62**
Right SF	−0.13	0.24	−0.44*
Left+right SF	−0.32*	0 15	−0.67**
Left PT	−0.38*	0.02	−0.66**
Right PT	−0.11	0.24	−0 36
Left+right PT	−0.28	0.17	−0.64**
Posterior mid-body (normalized)			
Left SF	−0.21	−0.29	−0.07
Right SF	−0.41**	−0.27	−0.59**
Left+right SF	−0.38*	−0.35	−0.38
Left PT	−0 27	−0.31	−0 14
Right PT	−0.43**	−0.24	−0.66**
Left+right PT	−0.43**	−0.33	−0.50*

*Indicates $P < 0.05$; **indicates $P < 0.01$. Abbreviations as in previous tables.

and left measurements, it was found that in males not only the left SF had a strong negative correlation to the anterior mid-body, but it was also found that the right SF had a strong negative correlation with the posterior mid-body (see Table 6).

Planum temporale area estimations showed a close similarity to SF distance in their correlations with the anterior and posterior mid-body (Table 6). For example, normalized anterior mid-body area correlated strongly with the left+right plana of males, but not of females (*see* Fig. 5). Other callosal regions did not show a significant correlation with SF or PT size in any of the sexes.

Summarizing, in males normalized anterior mid-body area may be determined by the size of the left SF (or PT), and normalized posterior mid-body area may be determined by the size of the right SF (or PT). In females these relationships are non-significant. This finding resembles the inverse correlation between SF (or PT) asymmetries and isthmus size that was found preferentially for males. Together, these findings suggest that a closer relationship between perisylvian areas and callosal structure may exist in males than in females.

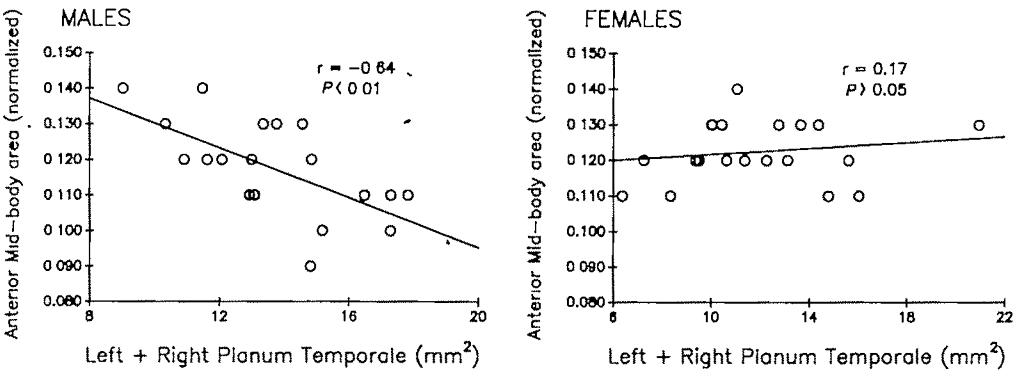

FIG. 5. Plots of left+right planum temporale areas against the normalized area of the anterior mid-body of the corpus callosum Females and males are shown separately. The least-squares regression lines are also shown.

DISCUSSION

Asymmetries in the perisylvian areas

Procedures for measuring the Sylvian fissure and planum temporale. Given the absence of methodological information about the measurement of the length of the Sylvian fissure and planum temporale (Geschwind and Levitsky, 1968; Galaburda *et al.*, 1978, 1987), we decided to report our observations in this material. We have improved the accuracy of measuring the length of the planum temporale by tracing the curved distance between Heschl's first gyrus and the end of the Sylvian fissure (SF). This method differs from Geschwind and Levitsky's (1968) procedure, which consisted of tracing the straight distance between Heschl's gyrus and the posterior end of the Sylvian fissure, as seen from pictures of the superior surface (Fig. 2).

The posterior end of the Sylvian fissure is difficult to determine because it bifurcates into a superior and an inferior branch as it approaches the parietal lobe (*see* Materials and methods). Previous studies have not specified which branch has been used for planum temporale measurements. As stated in Materials and methods, we measured both the superior and the inferior branches of the Sylvian fissure. It was found that in most cases the superior branch was longer than the inferior one or similar in size. There were only three exceptions (out of 80) to this pattern, where the inferior branch was longer, and those cases always occurred in the left hemisphere (two females, one male). Therefore, the superior branch, being usually longer than the inferior one or similar to it in size, may correspond adequately to the Sylvian fossa. In those cases where the inferior branch was longer than the superior, we preferred to measure the shorter superior branch on the grounds that homotopic cortical regions would tend to be located in corresponding branches of the Sylvian fissure, regardless of their relative lengths.

We did not directly quantify the area of the planum temporale as Galaburda *et al.* (1987) did because it was not clear which end of the fissure was to be used to make the incision to expose the planum. As has been stated before (Witelson and Kigar, 1987, 1988; Witelson, 1990), it is not always clear where the end of the Sylvian fissure is. Furthermore, it has been argued that the planum temporale is actually a curved structure and that there is some error in measuring its area from pictures of the superior surface of the temporal lobe (Witelson and Kigar, 1987, 1988; *see also* Fig. 1).

The estimations of the area of the planum temporale (PT) fitted well with those of the Sylvian fissure (SF) measurements. These results, together with the observed lower variance of the depth of the planum temporale (DPT) measurements, permit us to suggest that most of the variation in size of the planum temporale is produced by the length of the Sylvian fissure. Also, the results obtained when using estimations of planum areas closely resemble the results obtained with SF measurements (*see* Table 3).

We conclude that the curved SF distance is a good estimator of the size of the planum temporale, since (i) it seems to be the main dimension of variability in this region; (ii) errors due to projection of the curved planum on a plane [as done by Geschwind and Levitsky (1968) and Galaburda *et al.* (1987)] are minimized; (iii) it is possible in this way to avoid confusion in regard to the branch of the Sylvian fissure used for measuring the planum temporale. With this method, both branches are accessible to measurement.

Size dependency. The length of the Sylvian fissure did not depend significantly on brain weight, although both the depth of the planum temporale (DPT) and its area (PT) showed a marginally significant dependency on brain weight. However, the significance of the correlations disappeared after separating the sexes.

When correlating absolute asymmetry values $|\text{left}-\text{right}|$ with the sum of left plus right (Table 2) we did not see any significant size effect, excepting the case of DPT. These findings are reported in the context of previous reports proposing that asymmetries in the planum temporale are inversely correlated to the sum of left and right values (Galaburda *et al.*, 1987). Our disagreement with these authors is most likely due to the asymmetry measure used. Galaburda *et al.* (1987) used an asymmetry coefficient $|\text{left}-\text{right}|/(\text{left}-\text{right})$ instead of the raw differences in size $|\text{left}-\text{right}|$, as we did. Using our data, the asymmetry coefficient also shows a significant, negative correlation with $(\text{left}+\text{right})$. However, we interpret this as a consequence of the weak correlation between $|\text{left}-\text{right}|$ and $(\text{left}+\text{right})$ we observed. In this case, as $(\text{left}+\text{right})$ increases, the asymmetry coefficient |left−right|/(left+right) will tend to decrease because |left−right| will not change much in any direction. The result will largely reflect the negative correlation between (left+right) and 1/(left+right).

Contribution of the two sides to the asymmetries. We studied the relative contributions of the left and the right sides to the differences in size between them. It was found that in SF and PT measurements there were no significant differences between the contribution of the two sides to the asymmetries (Table 3). This indicates that both sides may be important in determining the degree of asymmetry.

In the case of DPT measurements, the smaller side was determinant in the production of asymmetries in both leftward and rightward asymmetric brains, the difference between sides being significant only in leftward asymmetric brains (Table 3). In other words, the smaller side correlated better with asymmetries. However, DPT measurements are less variable than SF and PT measurements and are regarded as less reliable indices of the size of the planum temporale.

In other words, we did not detect an overall dependency of perisylvian asymmetries on the size of either side. In the case where it was detected, the smaller side determined the asymmetry level, as predicted by Galaburda *et al.* (1987).

As we pointed out, our asymmetry measurement was just the difference between left and right, while Galaburda *et al.* (1987) used the asymmetry coefficient mentioned above. Again, we did not use the asymmetry coefficient in order to avoid a built-in bias of the asymmetry coefficient, which tends to produce a high negative correlation with the smaller side and a weak positive one with the larger side.

Sex differences in the Sylvian fissure and planum temporale. No significant sex differences in the SF (left, right or both) were observed, despite a robust difference in brain weight between the sexes. This may be interpreted as due to the high variance of the SF measurements. Depth of the planum temporale measurements, having a lower variance, showed a significant overall sex effect. In terms of asymmetries, we did not detect sex differences in the measurements of SF and PT, and the differences were larger but still non-significant in the case of DPT. These findings do not agree with Geschwind and Galaburda (1985) and with Galaburda *et al.* (1990), who theorize that females would show larger anatomical asymmetries than males. The results also disagree with Wada *et al.* (1975) and with McGlone (1980), who claim that males show larger anatomical asymmetries than females.

The corpus callosum: sex differences and relationship to Sylvian fissure

The corpus callosum: sex and size dependency. There have been several conflicting reports regarding sex differences in overall callosal size. In our sample, all the sex differences in callosal size were in favour of males, and tended to disappear when corrected for differences in brain weight (Table 4). On this point we agree with Witelson (1989) and with Clarke *et al.* (1989), who found small sex differences in the overall size of the corpus callosum, which disappeared when correcting for brain size (Table 7). Other authors have also failed to find sex differences in overall size of the callosum (de Lacoste-Utamsing and Holloway, 1982; Weber and Weis, 1986; Yoshii *et al.*, 1986; Kertesz *et al.*, 1987, 1990; Byne *et al.*, 1988; Demeter *et al.*, 1988; O'Kusky *et al.*, 1988; Weis *et al.*, 1989; Clarke, 1990; Elster *et al.*, 1990; Allen *et al.*, 1991).

TABLE 7 SUMMARY OF THE MAIN FINDINGS OF THIS STUDY AND THEIR RELATIONSHIP WITH SELECTED PREVIOUS STUDIES

	Present study	*Rosen et al. (1989), Galaburda et al. (1987, 1990)*	*Witelson (1985, 1990), Witelson and Kigar (1988)*
Correlations between side and asymmetries	Right side	Smaller side	
Sex difference in asymmetries	–	+	–
Sex difference in isthmus	–		Females > males
Sex difference in splenium	–		–
Inverse relationship between callosum and asymmetries	Isthmus and SF asymmetries	Callosal terminals and SMI asymmetries	Callosal size and handedness
Sex difference in brain organization	Males only. SF size and asymmetry correlate with callosum	Males interhemispheric Females: intrahemispheric	Males only: handedness effects in callosum

+ indicates positive findings, – indicates negative findings SMI asymmetries = asymmetries in somatomotor cortex. Other abbreviations as in previous tables.

Witelson (1989) and Clarke (1990) found a sex difference in the isthmus in favour of females, especially among right-handers. We did not see this effect in our sample. Rather, males had a larger isthmus than females, a difference that disappeared when correcting for brain size (Table 4). Clarke (1990) also found that a measure of the minimal callosal width (*see* Materials and methods) was larger in females than in males if normalized for total callosal size. We found the reverse pattern, although the difference was non-significant. The differences with Clarke (1990) might be explained in virtue of (i) a different methodology for measuring callosal size (we used post-mortem material and Clarke used MRIs), and/or (ii) a different sampling procedure (our subjects were derived from the general population in Chile, while Clarke's were graduate students at UCLA), which among other things resulted in populations of different age ranges. In our sample, the mean age was 46.8 yrs, with a range of 25–60 yrs, while in Clarke's sample, the mean age was 28.2 yrs, with a range of 21–43 yrs. No sex differences in the area of the splenium corrected for total callosal area, as suggested by Clarke *et al.* (1989), were found either. This latter result agrees with Oppenheim *et al.* (1987), Byne *et al.* (1988), Reinarz *et al.* (1988), Witelson (1989) and Clarke (1990). Therefore, regarding sex differences our results were rather conservative. No sex differences were found in callosal size or shape.

We did find a dependency of total callosal area on brain size (Table 5), in the same direction as Witelson (1989). The significance of this relationship disappeared after separation according to sex, but our results agree with Witelson (1989) in that the correlation of callosal size with brain size is stronger in males than in females (in both studies these relationships were non-significant). In the present study, the size dependency was concentrated in the genu of males (Table 5). Other authors did not find a significant relationship between callosal area and brain weight (Demeter *et al.*, 1988). Kertesz *et al.* (1987), Elster *et al.* (1990) and Clarke (1990) found no correlation between callosal area and midsagittal brain area as seen in MRI.

The relationships between callosal size, brain weight and sex remain controversial.

It may be that sampling differences and the different methodologies used to measure callosal area (post-mortem material as opposed to MRI) explain part of the disagreements. It is likely that much larger samples of material are still needed to ascertain these relationships. In this context it is worth mentioning the work of Haug (1987), who reported that the larger cortex of human males has a lower cell density than the smaller cortex of human females, leading to a similar number of cortical neurons in each sex. If this is the case, it would not be surprising that there are no sex differences in callosal area, since similar numbers of neurons would project through the callosum.

Callosal size and fibre composition of the corpus callosum. It still must be resolved what an increase in the area of a particular callosal region implies in terms of fibre composition. Recently, LaMantia and Rakic (1990) counted fibres in the corpus callosum of the macaque, as seen in electron microscopy. They report that no correlation exists between callosum area and total numbers of fibres, as well as noting a twofold variation in total numbers of fibres across subjects. From their data, we calculated that the average axon density in each subject correlates negatively with callosal area ($r = -0.73$, $P < 0.05$, $n = 8$), which indicates that variation in callosal area results from changes in fibre densities (however, note that their sample is very limited in size). This seems to indicate that variation in callosal area results from either an increase in interfibre distance or an increase in axon size. A recent study (Aboitiz, 1991) suggests that in humans a rather different relationship holds between callosal area and fibre numbers, as seen in light microscopy. A strong, positive correlation between total numbers of fibres and callosal area emerged ($r = 0.88$, $P < 0.01$, $n = 20$), while a non-significant correlation existed between fibre density and callosal area ($r = 0.27$, $P < 0.05$, $n = 20$). Note that about 20% of the total fibres are not detected by the light microscopy method, due to their small diameter (less than 0.4 μm; Aboitiz, 1991). Therefore, fibre counts under light microscopy represent only a fraction of the total numbers of callosal fibres, which can be detected using electron microscopy. It is possible that this explains the differences between the two reports, but it is also necessary to consider the differences in sample size in the two studies: in the macaque study (LaMantia and Rakic, 1990), $n = 8$; and in the human study (Aboitiz, 1991), $n = 20$.

Asymmetries and the corpus callosum. We now turn to one of the most intriguing findings of this study, i.e. a possible anatomical relationship between brain asymmetries and callosal structure in humans. These findings bear direct relevance to the debate on the relationship between brain lateralization and interhemispheric communication (Witelson, 1985, 1989; Kertesz *et al.*, 1987, 1990).

In males, we found a correlation between the magnitude (not direction) of asymmetries in perisylvian areas and the size of the isthmus of the corpus callosum (Fig. 4), which apparently includes fibres connecting these areas (de Lacoste *et al.*, 1985; Pandya and Seltzer, 1986).

This result agrees wtih the findings of Rosen *et al.* (1989, 1990) that in the somatomotor cortex of the rat the density of callosal projections decreases with increasing asymmetries. As Galaurda *et al.* (1990) discuss, this may be the result of selective synaptic stabilization during cerebral cortex development (Changeux and Danchin, 1976). It may be that more asymmetric regions have (functionally and topographically) less homotopic points, a circumstance that may lead to a more extensive terminal retraction in the perinatal period

(Innocenti, 1986). This may result in greater interhemispheric isolation and in turn possibly higher intrahemispheric connectivity (Galaburda *et al.*, 1990).

Although the present findings concern specific portions of the corpus callosum, these results are generally in line with those of Witelson (1985, 1989). Using post-mortem material, this author found that in males, non-consistent right-handers tended to have larger callosal areas than consistent right-handers (Table 7). Considering that non-consistent right-handers represent a less lateralized population than consistent right-handers, these results agree with ours in general terms. We also agree with Witelson (1990) in that the relationships with callosum size were significant only in males. It must be noted that Clarke (1990) using a sample comparable in size to Witelson's (1990) (Witelson's sample was of 50 subjects, and Clarke's was of 60 subjects), failed to find a handedness effect in callosal size as seen in MRI. However, Witelson's (1990) non-right-handed subjects, unlike Clarke's, are mostly mixed handed. O'Kusky *et al.* (1988) also found a correlation between alleged right hemisphere language dominance and callosal size as seen in MRI, but callosal size was unrelated to handedness. Other authors also failed to find handedness effects in callosal size (Kertesz *et al.*, 1987; Reinarz *et al.*, 1988). As mentioned, Witelson (1989) argues that differences between studies may be partly due to different criteria for determining handedness.

Sylvian fissure length and the corpus callosum. Other intriguing results are the negative correlations between the anterior and posterior mid-body of the corpus callosum and the sizes of the left and right perisylvian areas in males (Table 6; Fig. 5). Interestingly, the anterior mid-body may include fibres from Broca's area (Pandya and Seltzer, 1986).

A tentative explanation for these findings is that in males, growth in perisylvian areas implies increased projections to more anterior, ipsilateral cortical regions (such as anterior language regions). Considering that long ipsilateral projections may compete with contralateral projections for synaptic targets (Galaburda *et al.*, 1990), the increase in ipsilateral connections might occur at the expense of commissural connections in these anterior areas. In turn, this would result in a decreased mid-body area in the callosum.

In males, the left Sylvian fissure had a stronger correlation with the anterior mid-body of the callosum, while the right Sylvian fissure had a stronger correlation with the posterior mid-body (Table 6). This difference may be tentatively attributed to a different connectivity of the left and right perisylvian areas of the human male brain. The left perisylvian regions (generally dominant for linguistic functions) might project to anterior ipsilateral areas located more rostrally than is the case for the right perisylvian regions. This would explain the negative correlation with more anterior callosal areas in the left than in the right perisylvian regions.

As suggested above, increased ipsilateral connections between language-related areas might produce a decrease in anterior callosal connections only in males. In turn, this may indicate that ipsilateral connections may become more abundant in males than in females. If a higher connectivity implies a more diffuse localization, this hypothesis would be consistent with Kimura and Harschman's (1984) concept of a more diffuse language representation in the left hemisphere of males than of females (however, *see* Kertesz and Benke, 1989).

Summarizing, the present results may indicate that commissural connections depend on the size and asymmetry of perisylvian regions only in males. This is consistent with a hypothesized tendency for an increased ipsilateral connectivity in the cerebral hemispheres of males.

Conclusions

In this study (i) we found no relationship between the degree of anatomical asymmetry |left−right| and the overall size of the planum temporale (left+right); (ii) we also failed to detect sex differences in either anatomical asymmetries or callosal area; (iii) we report a relationship between perisylvian areas and commissural connections limited to males: (*a*) there is a negative correlation between perisylvian asymmetries and the size of the callosal isthmus; (*b*) there is a negative correlation between the size of perisylvian areas and the normalized area of the mid-body of the callosum. These results bear on theories of sex differences in brain organization. Finally (iv), we also report that the anterior corpus callosum (genu) depends on brain weight only in males.

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CHANGES IN BRAIN FUNCTIONAL CONNECTIVITY IN ALZHEIMER-TYPE AND MULTI-INFARCT DEMENTIA

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SUMMARY

Clinical and neuropathological evaluation of elderly subjects with dementia has traditionally concentrated upon the focal distribution of brain disease, ignoring changes in the complex connections that link brain areas and that are crucial for cognition. We examined subjects with the two most common forms of dementia in the elderly (dementia of the Alzheimer type or DAT, and multi-infarct dementia or MID); and used electroencephalographic (EEG) coherence to examine the effects of these illnesses on the functional connections between brain areas. We studied coherence between brain areas known to be linked by two different types of connections: (i) dense narrow bands of long corticocortical fibres; (ii) broad complex networks of corticocortical and corticosubcortical fibres. Areas that were linked by dense narrow bands of long corticocortical fibres showed greatly diminished coherence in subjects with DAT; among MID subjects, this coherence was not significantly affected. Areas that were linked by broad connective networks showed the largest decreases in coherence among MID subjects. These findings are consistent with neuropathological evidence that Alzheimer's disease is a neocortical 'disconnection syndrome' in which there is a loss of structural and functional integrity of long corticocortical tracts. The findings further suggest that the vascular disease of MID most prominently affects broad fibre networks that may be more vulnerable to diffuse subcortical vascular damage. A ratio of coherence from complex corticocortical-corticosubcortical networks divided by coherence from long corticocortical tracts correctly classified 76% of subjects into DAT and MID categories. Overall, these results indicate that EEG coherence detects basic pathophysiological differences between subjects with DAT and MID, and that these differences may be clinically useful.

INTRODUCTION

Clinical and neuropathological evaluation of elderly subjects with dementia has traditionally concentrated upon focal signs of brain disease. The clinical observation of severe memory impairment in patients with dementia of the Alzheimer type (DAT), and neuropathological localization of senile plaque and neurofibrillary tangle formations in the hippocampi, implicate focal temporal lobe pathology and help to explain severe memory dysfunction (Cummings and Benson, 1983; Kemper, 1984). The spotty cognitive deficits observed in multi-infarct dementia (MID), and neuropathological findings of multiple areas and ischaemic disease and lacunar infarcts, substantiate an inconsistent

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process that may affect only a few cognitive functions, depending on which regions of the brain are damaged (Cummings and Benson, 1983; Holborn *et al.*, 1990).

The interpretation that brain lesions affect only locally mediated functions ignores a fundamental principle of brain organization: all cognitive tasks are subserved by many areas whose functions are integrated by a complex network of connections. Geschwind (1965) reviewed the work of Wernicke (1874), Déjerine (1892) and Liepmann (1898, 1900), and revived interest in the 'disconnection syndromes'. He described these as profound cognitive losses, such as aphasia, agnosia, or apraxia, that resulted from disruption of the structural connections between functionally related cortical areas.

There is ample neuropathological evidence to suggest that disruptions in brain connectivity have a central role in the cognitive deficits seen in DAT and MID. The senile plaques and neurofibrillary tangles of DAT prominently involve the origins and terminations of the long corticocortical associative fibres of the brain (Pearson *et al.*, 1985; Rogers and Morrison, 1985; Esiri *et al.*, 1986; Lewis *et al.*, 1987). The location of the neuropathological changes led Morrison *et al.* (1986) to hypothesize that Alzheimer's disease is a neocortical 'disconnection syndrome' where associative areas lose afferent and efferent connection through white matter tracts. This disconnection occurs at the cortical level and is associated with the death of pyramidal neurons that provide the long corticocortical projections (Pearson *et al.*, 1985; Lewis *et al.*, 1987).

Although clinical impressions indicate that MID is a 'spotty' process, with losses due to multiple discrete infarctions (Cummings and Benson, 1983), dementia appears to ensue only after a critical volume of brain tissue has been damaged or destroyed (Tomlinson, 1980; Wallin and Blennow, 1991). By the time dementia is present, damage is widespread with large areas of deep white-matter disease seen on computed tomography (CT) (Wallin *et al.*, 1989*a*), as well as significant demyelination and Wallerian degeneration in areas far removed from clear infarcts (Englund *et al.*, 1987; Brun, 1988; Wallin *et al.*, 1989*b*; Wallin and Blennow, 1991). While it is possible for a few strategically placed infarcts disrupting known association fibre pathways to cause a dementia syndrome (Ishii *et al.*, 1986; Kooistra and Heilman, 1988; Mendez *et al.*, 1989; Caplan *et al.*, 1990; Tatemichi, 1990), it is much more likely that MID follows from diffuse deep white-matter ischaemic disease that causes widespread demyelination and subcortical disconnection (Román, 1985, 1987; Lotz *et al.*, 1986; Ferszt *et al.*, 1987; Wallin and Blennow, 1991).

Electroencephalographic (EEG) coherence could well be a sensitive and selective method for assessing the integrity of structural connections between brain areas in demented patients. As a measure of shared electrical activity, coherence has been shown to monitor the function of connections between brain areas that are linked by relatively dense fibres (Busk and Galbraith, 1975; Thatcher *et al.*, 1986) or that are functionally related (Beaumont and Rugg, 1979). Methods similar to coherence, such as measurement of information transmission (Callaway and Harris, 1974) and correlation analysis (Gevins *et al.*, 1981), yield similar results: as linked cortical areas become involved in a task, the shared electrical activity between them increases selectively (Callaway and Harris, 1974; Gevins *et al.*, 1981). Coherence appears to be a reliable measure of the functional connections between brain areas, monitoring interactions between brain areas while subjects are at rest (Tucker *et al.*, 1986), involved in processing primitive non-verbal stimuli (Davis and Wada, 1974), performing arithmetic or visual-spatial tasks (Shaw *et al.*, 1977, 1978), or performing motor tasks (Busk and Galbraith, 1975; O'Connor and Shaw, 1978).

Two previous studies of subjects with DAT and MID have shown that these syndromes have different effects on coherence between brain regions, with increased coherence between some brain regions and decreased coherence between others relative to normals (O'Connor *et al.*, 1979; Leuchter *et al.*, 1987). No systematic pattern of difference between these groups of demented patients, linked to the underlying neuropathology, has yet been described.

We hypothesized that, given the differing neuropathology of DAT and MID, specific connections between brain regions would be affected primarily in each illness (and largely spared in the other illness); DAT and MID would therefore show significantly differing patterns of coherence. The disconnection hypothesis of Alzheimer's disease predicts that a group of DAT subjects should show selective decreases in coherence between areas that are connected by dense corticocortical fibres: these fibres should be systematically 'disconnected' by the neuropathology of DAT, and less affected by the non-specific damage and demyelination of MID. Conversely, the MID group should show changes in coherence where complex networks of connections involving corticocortical, corticostriate and corticothalamic fibres are responsible for linking brain areas. These networks, reliant on large volumes of white matter and involving loops of connections between cortical and subcortical structures, should be more sensitive to disruption by the subcortical vascular damage of MID. To test our hypotheses, we examined coherence *between* pre- and post-Rolandic areas (linked by long corticocortical fibres) and coherence *within* pre- and post-Rolandic areas (linked by complex networks of connections). The hypotheses predict that the coherence between areas separated by the Rolandic fissue would be decreased primarily among DAT subjects, while coherence within pre- or post-Rolandic networks would be decreased primarily among MID subjects.

METHODS

Subjects

Subjects with dementia were recruited from patients undergoing evaluation for dementia at the UCLA Neuropsychiatric Hospital; controls were spouses of patients or were recruited from the community. All control subjects gave informed consent to participate in this study; for testing of subjects with dementia, informed consent was obtained both from the subject and a family member or legal guardian. Procedures were approved by the Human Subjects Protection Committee of the UCLA School of Medicine.

All subjects were at least 60 yrs of age and had received no medications known to affect central nervous system function for at least 10 d prior to the time of their EEG. Control subjects with any prior history of mental illness were excluded, as were control or demented subjects with confounding factors that might affect brain function (e.g. history of head trauma, cranial surgery). Subjects underwent a comprehensive evaluation for dementia, including a history, physical examination, relevant laboratory tests (Cummings and Benson, 1983) and either a CT or magnetic resonance imaging (MRI) study of the brain.

Demented subjects were diagnosed according to DSM-III-R criteria for primary degenerative DAT and MID (Leuchter *et al.*, 1987), modified as follows: all DAT subjects were required to satisfy the criteria proposed by McKhann *et al.* (1984) for probable Alzheimer's disease, and all MID subjects were required to have a Hachinski Ischemia Scale (Hachinski *et al.*, 1974) score greater than seven, or evidence of infarction or ischaemic damage on CT or MRI scanning.

There were 49 subjects meeting criteria for DAT, 29 for MID and 38 for controls. There was no significant difference in the mean ages of the DAT and control groups, although the MID group was slightly older (72 ± 8, 72 ± 8 and 78 ± 7 yrs, respectively; all numbers represent mean ± SD). The overall gender ratio for the three groups was 1.7 : 1 (F : M), with a nearly equal ratio in the control group (1.1 : 1) and more females in the DAT and MID groups (2.2 : 1 and 1.9 : 1, respectively). All subjects underwent a Folstein mini-mental state examination within 2 d of their EEG (Folstein *et al.*, 1975). There was no significant difference in the level of cognitive impairment between the DAT and MID groups as judged by the Mini-Mental State Examination scores, although both the demented groups differed in both mean and standard deviation from the control group (17.5 ± 7.4, 15.7 ± 8.8 and 29.3 ± 1.3, respectively). The mean Hachinski score for the MID group (5 ± 2.4) was significantly higher than that for the DAT or control groups (2.4 ± 1.4 and 0.5 ± 2.4, respectively) ($P < 0.0001$), with seven (28%) of the MID subject having scores of seven or greater, six (24%) of the MID subjects having a score of six, and no DAT or control subjects having a score greater than five.

Five of the MID subjects had evidence of cortical infarction, and seven had evidence of lacunar infarction on CT or MRI scanning. The remaining subjects had either patchy areas of high-signal white-matter lesions on T_2-weighted MRI images, or areas of decreased density on CT scanning. None of the DAT or control subjects had evidence of cortical infarction, and only one control subject had evidence of a lacunar infarct. Large white-matter lesions were much less common among the DAT subjects (8/49, or 16%) and the control subjects (3/38, or 8%) than among the MID subjects (22/29 or 76%).

Electroencephalogram procedures

Electroencephalograms were performed by trained technicians using standard clinical procedures, with electrodes applied using the International 10-20 System. The EEG was recorded using a Nihon-Kohden 4317 electroencephalograph. Sixteen channels of EEG data were collected using a montage of four longitudinal electrode chains (two temporal, two parasagittal) which sampled brain electrical activity in all major regions: Fp2-F8, F8-T4, T4-T6, T6-O2, Fp1-F7, F7-T3, T3-T5, T5-O1, Fp2-F4, F4-C4, C4-P4, P4-O2, Fp1-F3, F3-C3, C3-P3 and P3-O1. Eye movements were monitored using anterior scalp electrodes and a right infraorbital electrode referenced to the right ear.

Quantitative data collection

A total of 5 min of quantitative EEG data were collected from each subject while they rested in the eyes-closed, maximally alert waking state. Data were collected for 32 s periods of time, after each of which data collection was suspended and the patient vigorously re-alerted. If drowsiness occurred in the midst of a 32 s data collection period, data collection was suspended immediately and the patient re-alerted as necessary.

Data were digitized and analysed using the FACT system (for Frequency And Coherence Topography) that has been described previously (Leuchter *et al.*, 1987). Sixteen channels of data were digitized at a rate of 128 points per channel per second, and collected in 4 s epochs. A technician subsequently eliminated epochs contaminated by muscle, eye movement or other artefacts, or by the appearance of drowsiness. Spectral analysis of the data was performed using a discrete Fourier transformation. The first nine 4 s epochs (a total of 36 s) of artefact-free data were processed and averaged to obtain a frequency spectrum for that individual.

Calculation of coherence

Coherence is a quantitative measure of similarity between signals in a given frequency band. It is analogous to the square of a correlation coefficient between two channels of EEG data x and y (Shaw, 1984), with a high coherence value (near 1) indicating that the channels analysed have considerable shared activity; a low value (near 0) indicates that shared activity is nearly absent. Coherence is defined as a function of the power spectral outputs for the two channels at any given frequency λ:

$$C_{xy}(\lambda) = \frac{|S_{xy}(\lambda)|^2}{S_x(\lambda) * S_y(\lambda)}$$

or the square of the cross-spectrum of the two channels x and y divided by the product of the spectra of the individual channels.

Coherence may be calculated between referential or bipolar pairs of EEG channels. In this study, coherence was calculated between pairs of bipolar channels. Bipolar electrode channels probably better represent the origins and terminations of white-matter tracts than referential pairs, which include origins, terminations and arbitrary reference points. Furthermore, several investigators have suggested that the use of common reference data renders the results of coherence calculations virtually uninterpretable (French and Beaumont, 1984; Fein *et al.*, 1988).

Electroencephalographic coherence values were calculated for each of five frequency bands, each 4 Hz wide, between 2 Hz and 22 Hz (2–6, 6–10, 10–14, 14–18 and 18–22 Hz), and between each pairing of EEG channels. The coherence in the 0–2 Hz band was excluded from analysis because of the likelihood of contamination by subtle eye movement or other motion artefact. Coherence in bands above 22 Hz was excluded because of the low power in those bands.

Selection and grouping of coherence variables

Thatcher *et al.* (1986) introduced the paradigm of averaging coherence among multiple recording sites that overlie the distribution of known corticocortical fibres to measure the electrical activity transmitted through those fibres. We utilized this paradigm to monitor the functional integrity of two major classes of cortical connectivity: long dense corticocortical fibre tracts (exemplified by the superior longitudinal fasciculus), and complex networks of corticocortical and corticosubcortical fibres (exemplified in the post-Rolandic area by the projections of the visual pathway, and in the pre-Rolandic area by the projections of the prefrontal cortex).

To measure the coherent brain electrical activity mediated by these fibre tracts, we first approximated the cortical distribution of the tracts on the convexities of the brain in relation to EEG electrode position. For example, we estimated that the superior longitudinal fasciculus connects the parietal cortex primarily underlying electrode P3 with the cortex underlying the anterior electrodes Fp1, F3 and F7 on the left (and electrode P4 with the anterior electrodes Fp2, F4 and F8 on the right). There also are strong reciprocal innervations from the prefrontal and frontal cortex underlying electrodes Fp1 and F3 to the cortex underlying the posterior electrodes P3, T5 and O1 on the left (and from Fp2 and F4 to the posterior electrodes P4, T6 and O2 on the right). We then determined which pairs of EEG channels most closely approximate this distribution, and averaged these pairs to determine the 'mean coherence' transmitted by the superior longitudinal fasciculus in both the postero-anterior (FASCICLE-PA) and antero-posterior (FASCICLE-AP) directions. The pairings of channels chosen to represent FASCICLE-PA, FASCICLE-AP, the visual pathway (VISUAL) and prefrontal cortex (FRONTAL) are listed in Table 1, and are shown graphically in Fig. 1.

Data analysis

After the individual variables were grouped and averaged as listed above, we performed a logarithmic transformation of the mean coherence variables to minimize problems with skewness and kurtosis (Pollock *et al.*, 1990). Log transformation was highly effective in normalizing the distribution of the coherence values (data not presented). All coherence variables were multipled by 10 prior to log transformation to eliminate negative values.

Linear regression was used to examine the relationships of coherence variables with mini-mental state examination and age (BMDP Biomedical Computer Programs, 1988). Differences in means between the three groups of subjects were examined in a pairwise fashion using *t* tests. The coherence in the DAT and MID groups also were calculated as a percentage of the means of the control group in each measure and frequency band, and displayed graphically in a frequency spectrum showing deviation from the mean for normals.

RESULTS

Coherence mediated by long corticocortical connections

In the FASCICLE-PA and -AP coherence measures, the DAT subjects' mean coherence values were consistently lower than those of the MID subjects in every frequency band, and lower than the control subjects in all but the 2–6 Hz band (Figs 2, 3). The MID subjects had several mean coherence values that were lower than the control subjects, but these differences were not statistically significant (Table 2).

TABLE 1 CHANNEL PAIRINGS SELECTED FOR AVERAGING TO CREATE MEAN COHERENCE MEASURES

Anatomic pathway (abbreviation)	*Electrode(s) of origin*	*Electrodes of termination*	*Averaged channel pairings*
Superior longitudinal fasciculus, postero-anterior projection	P3 (left)	F3, Fp1, F7	P3-O1/F3-C3 P3-O1/Fp1-F3 P3-O1/Fp1-F7
(FASCICLE-PA)	P4 (right)	F4, Fp2, F8	P4-O2/Fp2-F4 P4-O2/Fp2-F8 P4-O2/F4-C4
Superior longitudinal fasciculus, antero-posterior projection	Fp1, F3 (left)	P3, O1, T5	Fp1-F3/C3-P3 Fp1-F3/P3-O1 Fp1-F3/T5-O1
(FASCICLE-AP)	Fp2, F4 (right)	P4, O2, T6	Fp2-F4/C4-P4 Fp2-F4/P4-O2 Fp2-F4/T6-O2
Visual pathway projections	O1 (left)	P3, T3, T5	P3-O1/P3-C3 P3-O1/T3-T5
(VISUAL)	O2 (right)	P4, T4, T6	P4-O2/P4-C4 P4-O2/T4-T6
Prefrontal cortex projections	Fp1 (left)	F3, F7	Fp1-F3/F3-C3 Fp1-F3/Fp1-F7
(FRONTAL)	Fp2 (right)	F4, F8	Fp2-F4/F4-C4 Fp2-F4/Fp2-F8

Coherence mediated by pre- and post-Rolandic networks

In the VISUAL measure, the MID subjects' mean coherence values were lower than those found among the groups of DAT or control subjects in all frequency bands (Fig. 4). The DAT subjects' coherence was significantly lower than control subjects at only the 8 Hz band; the MID subjects, however, were significantly decreased compared with controls in the 8 Hz band, and significantly lower than the control and DAT subjects in the 12 Hz band (Table 3). In the FRONTAL measure, while the MID subjects' coherence was decreased relative to DAT and control subjects in most frequency bands (Fig. 5), these differences were generally not statistically significant (Table 3).

In both the VISUAL and FRONTAL measures in the 2–6 Hz band, the DAT subjects showed increased coherence compared with controls, while the MID subjects were decreased (Figs 4, 5). This difference approached statistical significance in VISUAL, and was significant in FRONTAL (Table 3).

Relationship between cognitive impairment and coherence

For most coherence variables, there was no significant association with cognitive status. In the FASCICLE-PA and -AP measures, there were no associations with mini-mental state examination scores among the DAT subjects at any frequency band; among the MID subjects, however, there was one moderate negative correlation. In the VISUAL and FRONTAL measures, there were no significant associations with mini-mental state examination scores among the MID subjects; there were, however, two moderate positive associations among the DAT subjects in the VISUAL measure (Table 4).

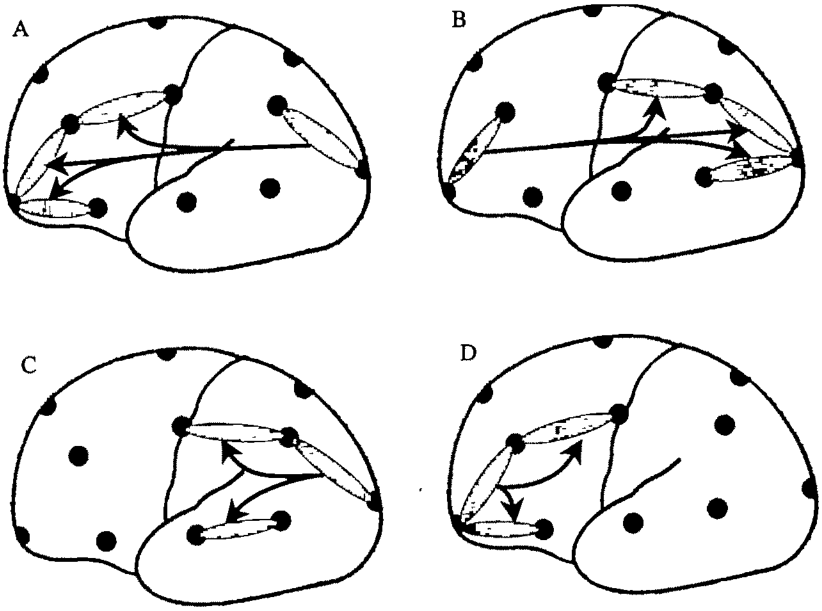

FIG. 1. Electrode sites for mean coherence calculations. Coherence variables were grouped in four combinations, denoted by (A) FASCICLE-PA, (B) FASCICLE-AP, (C) VISUAL and (D) FRONTAL. Data from EEG were analysed for indicated electrode pairs (the electrodes linked by shaded ellipses), and mean coherence values were calculated between the pairs that followed known white-matter tracts (depicted by heavy arrows); these coherence values were averaged to measure mean coherence associated with each tract. For clarity, only left hemispheric groupings are shown; homologous groupings for the right hemisphere also were used.

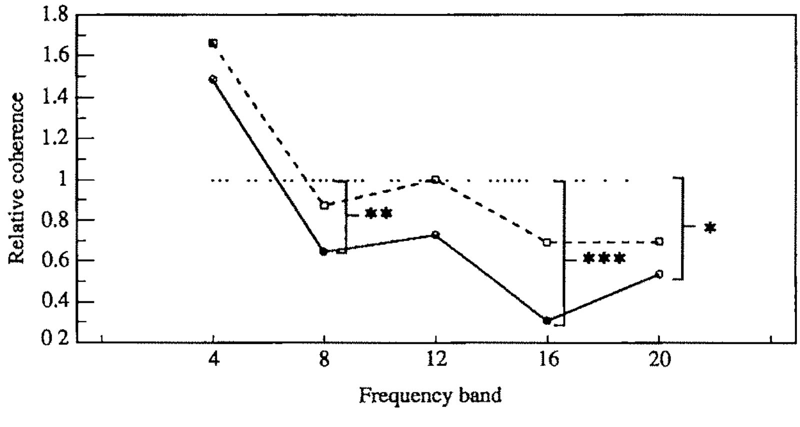

FIG. 2. Frequency spectrum of coherence for FASCICLE-PA measure. Coherence is displayed for the DAT (○) and MID (□) groups as a proportion on the mean value for the control group. Mean value for the control group is standardized to 1 in each frequency band, and indicated by the dotted line across the middle of the figure. Frequency bands are displayed across the bottom of the figure, with numbers representing the centre frequency of each band (i.e. '4' represents the 2–6 Hz band, '8' represents the 6–10 Hz band, etc.). *Difference between DAT and control subjects, $P < 0.05$; **difference between DAT and control subjects, $P < 0.01$; ***difference between DAT and control subjects, $P < 0.005$.

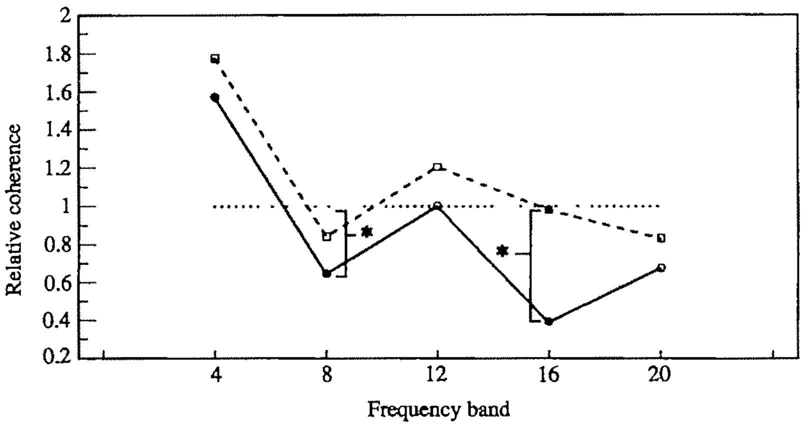

FIG. 3. Frequency spectrum of coherence for FASCICLE-AP measure. Coherence is displayed for the DAT (○) and MID (□) groups as a proportion of the mean value for the control group. Mean value for the control group is standardized to 1 in each frequency band, and indicated by the dotted line across the middle of the figure. Frequency bands are displayed across the bottom of the figure, with numbers representing the centre frequency of each band (i.e. '4' represents the 2–6 Hz band, '8' represents the 6–10 Hz band, etc.). *Difference between DAT and control subjects, $P < 0.05$.

TABLE 2. LONG CORTICOCORTICAL CONNECTIONS: COHERENCE DIFFERENCES BETWEEN CONTROL, DAT AND MID SUBJECTS

		Control (n = 38)		*DAT (n = 49)*		*MID (n = 29)*	
Measure		*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Fascicle-PA	4	0.06	0.09	0.08	0.12	0.09	0.11
	8	0.27	0.17	0.17**	0.13	0.24	0.18
	12	0.22	0.19	0.16	0.16	0.22	0.14
	16	0.17	0.14	0.05***	0.14	0.12	0.14
	20	0.13	0.10	0.07*	0.12	0.09	0.11
Fascicle-AP	4	0.05	0.11	0.07	0.12	0.08	0.11
	8	0.23	0.19	0.15*	0.15	0.20	0.19
	12	0.17	0.22	0.17	0.16	0.20	0.13
	16	0.11	0.13	0.04*	0.15	0.11	0.14
	20	0.10	0.13	0.07	0.18	0.08	0.11

Group t tests were performed on log-transformed averages multiplied by 10; mean and standard deviation values are tabulated. All P values reported reflect Welch's separate variance t test comparisons between pairs of groups. *Difference from control group, $P < 0.05$; **difference from control group, $P < 0.01$; ***difference from control group, $P < 0.005$.

Relationship between age and coherence

For the FASCICLE-PA and -AP measures, age was not significantly correlated with coherence in any frequency bands; there was one modest negative association among the MID subjects. For VISUAL and FRONTAL measures, there were several weak to moderate negative associations with age in the MID and control groups at 4, 12 and 16 Hz in the VISUAL measure, with a single weak positive association with age in the DAT group at 6–10 Hz. There were also weak negative associations with age in both DAT and MID groups in the FRONTAL measure at 2–6 Hz (Table 5).

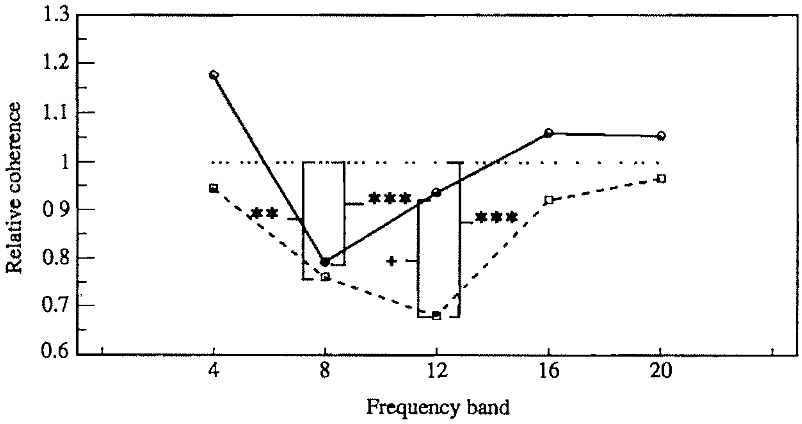

FIG. 4. Frequency spectrum of coherence for VISUAL measure. Coherence is displayed for the DAT (○) and MID (□) groups as a proportion of the mean value for the control group. Mean value for the control group is standardized to 1 in each frequency band, and indicated by the dotted line across the middle of the figure. Frequency bands are displayed across the bottom of the figure, with numbers representing the centre frequency of each band (i.e. '4' represents the 2–6 Hz band, '8' represents the 6–10 Hz band, etc.). **Difference between DAT and control subjects, $P < 0.01$; ***difference between DAT and control subjects, $P < 0.005$; $^{+}$difference between DAT and MID subjects, $P < 0.05$.

TABLE 3. NETWORK CONNECTIONS COHERENCE DIFFERENCES BETWEEN ELDERLY CONTROL, DAT AND MID SUBJECTS

		Control (n = 38)		*DAT (n = 49)*		*MID (n = 29)*	
Measure		*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Frontal	4	0.30	0.18	0.36^{+}	0.20	0.28^{+}	0.11
	8	0.27	0.17	0.23	0.12	0.21	0.15
	12	0.32	0.14	0.30	0.16	0.26	0.13
	16	0.29	0.16	0.28	0.20	0.22	0.12
	20	0.28	0.15	0.33	0.18	0.30	0.13
Visual	4	0.33	0.16	0.38	0.17	0.31	0.18
	8	0.61	0.19	0.48***	0.16	0.46**	0.23
	12	0.48	0.22	0.45^{+}	0.19	0.32^{+},***	0.21
	16	0.21	0.16	0.22	0.17	0.19	0.15
	20	0.20	0.15	0.21	0.15	0.19	0.14

Group t tests were performed on log-transformed averages multiplied by 10; mean and standard deviation values are tabulated. All P values reported reflect Welch's separate variance t test comparisons between pairs of groups. **Difference from control group, $P < 0.01$; ***difference from control group, $P < 0.005$; $^{+}$difference between DAT and MID subjects, $P < 0.05$.

Differences between DAT and MID subjects

While there were significant differences between the DAT and MID groups in the VISUAL coherence measure, on most measures there was overlap in the coherence values for the two groups of subjects. To study the potential clinical usefulness of coherence in distinguishing between DAT and MID subjects, we selected for further analysis those variables that showed the separation between DAT and MID groups: FASCICLE-PA coherence at 14–18 Hz, and VISUAL coherence at 10–14 Hz. Since

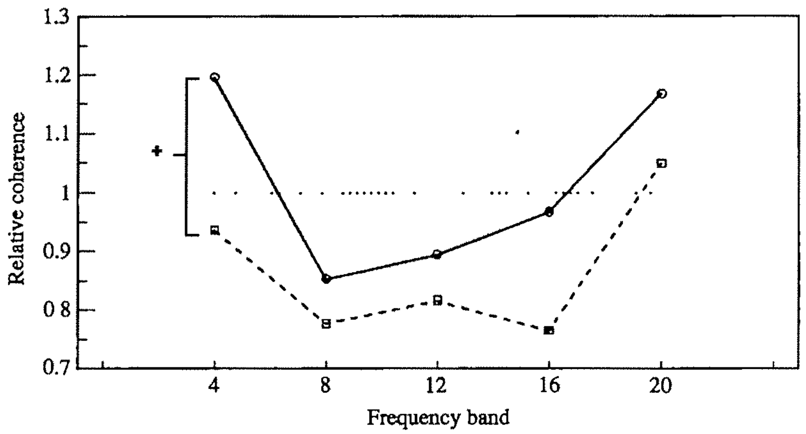

FIG. 5. Frequency spectrum of coherence for FRONTAL measure. Coherence is displayed for the DAT (○) and MID (□) groups as a proportion of the mean value for the control group. Mean value for the control group is standardized to 1 in each frequency band, and indicated by the dotted line across the middle of the figure. Frequency bands are displayed across the bottom of the figure, with numbers representing the centre frequency of each band (i.e. '4' represents the 2–6 Hz band, '8' represents the 6–10 Hz band, etc.). ⁺Difference between DAT and MID subjects, $P < 0.05$.

TABLE 4 RELATIONSHIP BETWEEN COHERENCE MEASURES AND COGNITIVE IMPAIRMENT

		DAT (n = 49)		*MID (n = 29)*	
Measure		*r*	*P*	*r*	*P*
Fascicle-PA	4	−0.12		−0.53	0.003
	8	−0.14		−0.05	
	12	0.15		−0.01	
	16	0.17		0.18	
	20	0.14		−0.04	
Fascicle-AP	4	−0.16		−0.23	
	8	−0.27		−0.15	
	12	0.11		−0.04	
	16	−0.09		0.18	
	20	0.08		0.23	
Frontal	4	−0.02		−0.32	
	8	−0.23		0.01	
	12	0.21		−0.16	
	16	−0.06		−0.26	
	20	−0.04		−0.25	
Visual	4	0.08		0.09	
	8	0.40	0.004	0.19	
	12	0.44	0.001	0.13	
	16	0.21		−0.04	
	20	0.44	0.001	0.13	

Linear regression models were used to assess the relationship between mini-mental state examination score and log transforms of the coherence measures multiplied by 10. Correlation coefficients (r) are tabulated, *P* values are also shown when they are significant at a level of less than 0.05.

TABLE 5. RELATIONSHIP BETWEEN COHERENCE MEASURES AND AGE

		Control (n = 38)		*DAT (n = 49)*		*MID (n = 29)*	
Measure		*r*	*P*	*r*	*P*	*r*	*P*
Fascicle-PA	4	−0.18		−0.01		−0.20	
	8	−0.16		0.16		−0.29	
	12	−0.17		0.13		−0.05	
	16	−0.15		0.21		0.28	
	20	0.05		0.23		0.17	
Fascicle-AP	4	−0.11		−0.13		−0.12	
	8	−0.12		0.06		−0.38	0.041
	12	−0.18		0.15		0.12	
	16	−0.12		0.07		0.35	
	20	0.19		0.25		0.31	
Frontal	4	0.14		−0.29	0.040	−0.40	0.033
	8	−0.08		−0.15		−0.30	
	12	−0.17		0.13		0.00	
	16	−0.02		−0.15		0.03	
	20	0.04		−0.10		0.05	
Visual	4	−0.49	0.002	−0.10		−0.38	0.045
	8	−0.23		0.30	0.04	−0.29	
	12	−0.32		−0.03		−0.47	0.011
	16	−0.34	0.039	−0.14		−0.41	0.028
	20	−0.37	0.007	−0.07		−0.10	

Linear regression models were used to assess the relationship between age and log transforms of the coherence measures multiplied by 10. Correlation coefficients (r) are tabulated; *P* values are also shown when they are significant at a level of less than 0.05.

one of the variables was greatly diminished in the DAT group (FASCICLE-PA) and the other in the MID group (VISUAL), we examined the distribution of the log of the ratio of these two variables (Fig. 6). The combination of these two variables yielded distinctly different distributions for the DAT and MID groups. Using a cut-off for the ratio of 0.18, 76% of the demented subjects were correctly classified as DAT or MID.

DISCUSSION

The examination of coherence between areas connected by known anatomical fibre tracts appears to detect not only differences between control and demented subjects, but also differences between subjects with DAT and MID. The DAT subjects had systematic decreases in coherence where long corticocortical fibres crossing the Rolandic fissure were involved; there was less effect on these coherence measures among the MID subjects. Conversely, when examining coherence within the pre- and post-Rolandic areas, there were more pronounced decreases in coherence among the MID subjects that appeared to distinguish them from DAT subjects.

This difference in coherence *between* pre- and post-Rolandic areas, versus *within* a pre- or post-Rolandic area, appears to be related to anatomic fibre distribution. The same posterior EEG channel (P3-O1) serves as the origin for both the FASCICLE-PA and the VISUAL coherence measures: the major difference between these measures is that the former terminates in the pre-Rolandic area, and the latter in the post-Rolandic area.

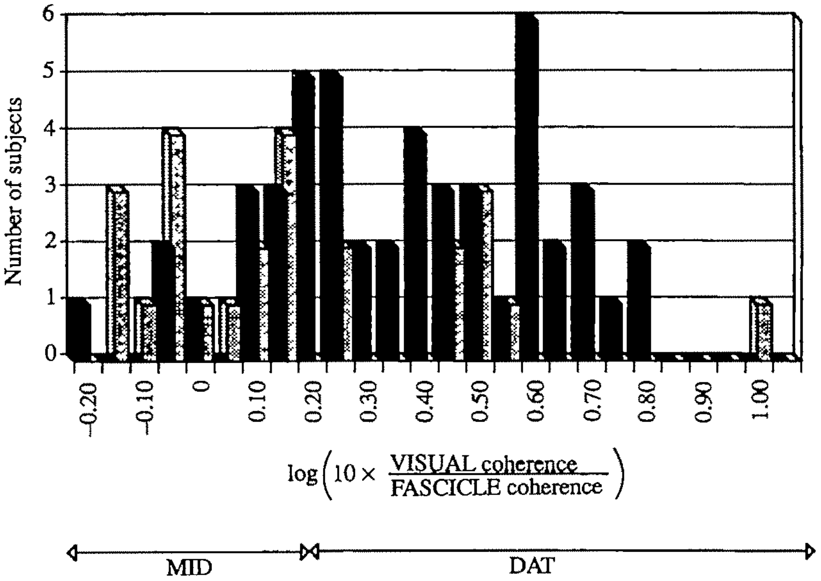

FIG. 6. Ratio of VISUAL coherence parameter (10–14 Hz) divided by FASCICLE-PA coherence parameter (14–18 Hz). Histogram of the distribution of values of the ratio for the two groups of subjects, with DAT subjects shown black and MID stippled. The arrows at the bottom indicate the cut-off of 0.18, with the majority of DAT subjects falling above and the majority of MID subjects below this point.

Neuropathological data support the interpretation of decreased coherence between pre- and post-Rolandic areas among DAT subjects as a selective disconnection of the long corticocortical tracts linking these areas. The primary connection between the pre- and post-Rolandic areas is the superior longitudinal fasciculus, a dense corticocortical fibre band connecting the parietal and frontal cortices (Truex and Carpenter, 1969; Jones and Powell, 1970; Goldman-Rakic, 1987, 1988; Fuster, 1989) and presumably mediating coherence (Thatcher *et al.*, 1986). Most of the fibres in this tract arise in layers II and III of the cortex (Jones, 1981). While the specific distribution of neuropathology does vary somewhat from patient to patient, these two laminae generally contain the highest areal concentration of senile plaque of any cortical layers; layer IV also contains a large number of amyloid plaques, although these tend to be smaller (Pearson *et al.*, 1985; Rogers and Morrison, 1985; Lewis *et al.*, 1987). Neuritic plaques generally show a strong predilection for layers II and III, with the neurofibrillary tangles most commonly seen in the pyramidal cells (Braak *et al.*, 1989; Delaere *et al.*, 1991). The prominence of this pathology in the layers of the associative cortex where fibres originate, and within the pyramidal cells that supply these fibres, is probably related to the degeneration of the long corticocortical fibres (Pearson *et al.*, 1985; Rogers and Morrison, 1985; Lewis *et al.*, 1987).

Degeneration of the long corticocortical tracts originating in laminae II and III may explain the asymmetric decrease in coherence, in which the rostral projection of the superior longitudinal fasciculus (FASCICLE-PA) shows much lower coherence than the caudal projection (FASCICLE-AP) in which the decrease in coherence is less pronounced. The rostrally projecting fibres follow a 'feed-forward' pattern, arising in the supragranular laminae (primarily II and III) of the parietal cortex and terminating primarily in layer IV of the frontal cortex. The caudally projecting fibres, however, follow a 'feedback' pattern, originating in both supra- and infragranular layers, and terminating in parietal cortex in laminae I and VI, avoiding layer IV (Maunsell and Van Essen, 1983; Van Essen and Maunsell, 1983; Selemon and Goldman-Rakic, 1985, 1988; Goldman-Rakic, 1988). Thus, the rostral projections arise in parietal cortex from superficial layers that are most severely affected by Alzheimer's neuropathology, and terminate in the frontal cortex in a layer that contains a high proportion of senile plaque (Rogers and Morrison, 1985). Conversely, the caudal projections originate in part from the infragranular layers that are less affected by Alzheimer's neuropathology, and terminate in the parietal cortex layers that have the lowest concentration of senile plaques and neurofibrillary tangles (Rogers and Morrison, 1985; Lewis *et al.*, 1987). The fibres projecting from the parietal cortex to the frontal cortex may therefore be more uniformly 'disconnected' than the reciprocal fibres projecting from the frontal to the parietal cortex.

The nature of connections crossing the Rolandic fissue are fundamentally different in structure from those that organize the flow of information within the pre- and post-Rolandic areas. Within the post-Rolandic cortex, complex networks of interneurons form cascades of connections between primary and associative visual cortex, as well as between cortical areas and the lateral geniculate and pulvinar thalamic nuclei that are related to visual processing (Peter, 1979; Rockland and Pandya, 1979; Desimone *et al.*, 1980; Van Essen and Maunsel, 1983). Within the pre-Rolandic cortex, similarly complex networks connect motor cortex with prefrontal cortex, and neuronal loops connect cortical areas with the dorsomedial and pulvinar thalamic nuclei (Goldman-Rakic and Porrino, 1985; Goldman-Rakic, 1988; *cf* Fuster, 1989). The complexity of the connections within the pre- and post-Rolandic cortices may make them much more susceptible to disruption by vascular damage than the superior longitudinal fasciculus. For example, connections between the primary and higher-order visual cortices are mediated by at least 33 different pathways according to animal studies, and rely upon many interneurons that traverse a large volume of cortex and white matter (Van Essen and Maunsell, 1983). The fact that the connections within these regions are more dependent on intermediate cortical areas and upon a rich network of interneurons suggests that vascular damage may be more likely to disrupt some portion of the network and thereby decrease coherence.

To be responsible for these substantial effects on coherence, the subcortical disease among MID subjects would have to be widely distributed, involving large volumes of white matter and significant demyelination and/or axonal destruction. Evidence from cerebral blood flow, electrophysiology, structural imaging and neuropathological studies suggests that such widespread white-matter disease is common in MID. Generalized functional impairment of white matter is supported by blood flow studies showing a global diminution of white-matter perfusion among MID subjects after correcting for atrophy and age (Kobari *et al.*, 1990), as well as by somatosensory evoked potential studies showing prolonged central conduction time in MID, but not in DAT (Abbruzzese *et al.*, 1984; Kato *et al.*, 1990). Generalized white-matter structural impairment has been documented by CT and MRI scanning (Bennett *et al.*, 1990; Bowen *et al.*, 1990; Kertesz *et al.*, 1990; Parnetti *et al.*, 1990), as well as by neuropathological studies of subjects with MID (Brun, 1988; Janota *et al.*, 1989; Peterson and Summergrad, 1989; Munoz, 1991).

These results suggest that coherence is largely uncomplicated by cognitive status as measured by mini-mental state examination scores; in the groups where the strongest effects of disease on coherence are seen (FASCICLE-PA and -AP for DAT subjects, and VISUAL and FRONTAL for MID subjects) there is no relationship with mini-mental state examination scores. This suggests that the changes in coherence that we report may be viewed as disease 'trait' measures that emerge relatively early in the course of illness and are stable over time. An alternative explanation is that there is a great deal of variability among individuals at any one level of cognitive impairment, so that a consistent relationship between the variables and cognitive impairment does not emerge. Longitudinal data will be necessary to explore this question further.

Corticocortical coherence mediated by long fibres also appears to be relatively insensitive to age in the more than 60 yr age group. This is unique among neurophysiological markers used to study dementia, most of which show a significant age effect. This finding differs from those which have been reported for EEG power measures, since the effects of age for these more conventional measures are generally similar to the effects of dementia, but of a lesser magnitude. For coherence, the effects of age and cognitive impairment appear to be distinct.

Local pre- or post-Rolandic coherence is affected by age to some extent, at least among the control and MID subjects. This is not surprising in the post-Rolandic area, since the mechanism regulating coherence in this region is presumably related to that which regulates the posterior dominant rhythm, that also is affected by age (Niedermeyer, 1987). Interestingly, the DAT group shows little age effect, except in one frequency band where it has the opposite sign (positive) of the age effect among control and MID subjects. This suggests that the DAT disease process overrides the age effect in this group; this interpretation is supported by the fact that in the same frequency band, the DAT group has a stronger positive association with mini-mental state examination scores.

The ratio of VISUAL to FASCICLE-PA coherence suggests that coherence may be clinically useful in distinguishing between the different dementia syndromes. The 76% accuracy that we report in categorizing subjects into DAT and MID clinical subtypes is encouraging, and compares favourably with the best classification that can be achieved using combinations of clinical signs and symptoms (Mölsä *et al.*, 1985; Ettlin *et al.*, 1989). The clinical differentiation between DAT and MID is problematic, however, and we do not have neuropathological confirmation of clinical diagnoses in these subjects. Such confirmation, along with replication of these findings on an independent sample of subjects, would help confirm the usefulness of our methods. Some portion of the 24% inaccuracy in the classification of these subjects undoubtedly arises from subjects with 'mixed' disease, since some subjects with dementia are found to have admixtures of DAT and MID pathology at autopsy. Such patients are extremely difficult to diagnose accurately on clinical grounds (Ettlin *et al.*, 1989), and coherence therefore may be particularly useful as a tool for assessing cases with mixed disease. Such subjects should be included in future studies of coherence.

Previous studies of coherence among subjects with dementia have examined pairings of individual EEG channels, not the averaged measures covering broader cortical areas on which we report here. Nevertheless, these results are largely consistent with earlier work on coherence in dementia. O'Connor *et al.* (1979) examined 24 elderly subjects with 'arteriosclerotic dementia', 'senile dementia' and depression. Diagnostic criteria for the former two conditions are not specified, but they may be comparable to our criteria for MID and DAT, respectively. O'Connor reported that coherence between the centroparietal area and the temporal area was lower among the arteriosclerotic than among the senile dementia subjects. Examination of the same channel pairing (C4-P4/T4-T6) among our subjects showed the MID subjects had lower coherence than DAT subjects; both were significantly lower than the control subjects (data not shown). O'Connor hypothesized that subjects with vascular dementia would have focal decreases in coherence related to the location of their vascular damage, and that the temporal region was more specifically damaged among these vascular dementia subjects. Our data suggest that such damage is prominent among MID subjects wherever short cortico-cortical and corticosubcortical fibres link brain areas; such connections are prominent between the parietal and temporal cortices (Goldman-Rakic, 1988).

O'Connor *et al.* (1979) also reported that coherence between the parieto-occipital and temporal cortices (P4-O2/T4-T6) was decreased both among vascular and senile dementia subjects at 10 Hz, and that this distinguished these subjects from those with depression. This observation is consistent with our data that DAT and MID subjects have significantly lower coherence than control subjects in the 6–10 Hz band.

The O'Connor group further observed that senile dementia subjects have slightly lower coherence than arteriosclerotic dementia subjects at 10 Hz in this same channel pairing. This observation appears to be at variance with our results showing that the MID subjects have lower coherence than the DAT subjects in all frequency bands in this channel pairing. The difference in mean coherence for the arteriosclerotic and senile dementia subjects reported by O'Connor for this brain area is negligible, however, and is based upon only 16 subjects. In our study, the difference between DAT and MID subjects in this channel pairing is smallest in the 6–10 Hz band (Fig. 3), approaching statistical significance in a lower band (2–6 Hz) and becoming highly significant in a higher band (10–14 Hz). This apparent inconsistency therefore may not reflect a true discrepancy in findings.

In another report on coherence among the demented elderly, our group (Leuchter *et al.*, 1987) previously reported increased coherence in high-frequency bands in the central head region among subjects with MID compared with DAT and control subjects. We continue to see this trend both in individual channel pairings and in the VISUAL coherence measure, although it does not reach statistical significance (data not presented). The reasons for the increased coherence in high-frequency bands among the MID subjects is unclear. According to the general hypotheses of this report, the MID subjects suffer disconnection of afferent and efferent fibres by white matter lesions, while the DAT subjects suffer disconnection primarily as a result of intrinsic cortical degeneration. It is possible the increased high frequency coherence is a non-specific finding in disconnected, non-degenerate cortex, which the DAT subjects do not exhibit because of cortical degeneration. This finding is not likely to be of clinical significance, however, since the between-group differences are not large.

Our findings generally are consistent with those of previous studies, suggesting that coherence may identify characteristics of the major dementing illnesses in the elderly. The neuroanatomical framework in which we have examined coherence suggests that the differences seen may be related to the differing distribution of neuropathology in the DAT and MID syndromes. The relative independence of these differences on the level of cognitive dysfunction or age suggests that they may be useful electrophysiological trait markers for the diagnosis of dementia. The high degree of accuracy of a combination of these variables in classifying subjects into the DAT and MID categories also suggests that this method for examining coherence may be useful for the differential diagnosis of patients with dementia.

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A CRITICAL APPRAISAL OF NEUROPSYCHOLOGICAL CORRELATES OF JAPANESE IDEOGRAM (KANJI) AND PHONOGRAM (KANA) READING

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SUMMARY

Owing to the Japanese language's unique writing system, which consists of phonograms and ideograms, reading impairments of Japanese brain-damaged patients have attracted the interest of many researchers. Past case reports as well as some widely accepted handbooks and textbooks have concluded that a specific aphasia type or lesion site is associated with a particular impairment pattern of phonograms and ideograms in reading. However, the methodology and analytical procedures in previous studies were inadequate for reliable generalizations to be made. First, the test materials were unspecified or inappropriate, or the number of test items was small. Secondly, the conclusions were presented without providing individual performance data to support them. Thirdly, in associating patterns of reading impairment with lesion sites, only single cases were reported.

The present investigation was designed to overcome the omissions of previous studies, and examined the ability to read 46 single phonograms and 46 single ideograms aloud in four groups of sufficiently large numbers of patients; namely, seven pure alexics, 23 Broca aphasics, 13 Wernicke aphasics, and seven patients with alexia and agraphia. Ours are the first data to demonstrate unequivocally no consistent linkage between aphasia type and the patterns of impairment of phonogram and ideogram reading. The impairment patterns were not uniform across patients even in the same aphasia group. A majority of the cases in each group showed that phonograms and ideograms were unselectively impaired. However, ideogram reading was more difficult in three cases in the pure alexia and Broca aphasia groups, respectively, and in one case in the Wernicke aphasia group. Phonogram reading was more severely disturbed in four cases among the Broca aphasics and in one case among the patients with alexia with agraphia. An apparent variability of impairment patterns characterized the Broca aphasic group.

These dyslexic patterns did not appear to correlate with the site and extent of lesions identified by computerized tomography scans. Past reports linking a particular impairment pattern of phonogram and ideogram reading and a specific lesion site were studies of single cases, and their conclusions seem oversimplified. While sensory and motor dysfunctions can usually be neuroanatomically localized in individuals, impairments of certain high cortical functions, such as the reading of phonograms and ideograms, may not be correlated with damage to definite neuroanatomical structures.

INTRODUCTION

The writing system of the Japanese language is distinct from those of Indo-European languages in that it consists of two types of letters, phonograms (kana) and ideograms

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(kanji). A phonogram represents a spoken syllable or 'mora', and the sound-to-script correspondence is strictly one-to-one. On the other hand, each ideogram represents a certain unit of meaning. Owing to this unique orthographic system, reading impairments of Japanese brain-damaged patients for phonograms and ideograms have attracted the interest of many researchers.

Of special interest in observing reading impairments of the Japanese language was the cases where reading of either phonograms or ideograms was less disturbed than that of the other type of script, resulting in what may be called a 'dissociation' between phonograms and ideograms. The concept of phonogram-ideogram dissociation in Japanese patients with certain types of aphasia or with damage to specific sites of the brain has been widely accepted, especially abroad. For example, some standard handbooks and textbooks state that reading of phonograms tends to be more impaired than reading of ideograms in Japanese patients with alexia with agraphia (or central alexia) (Benson, 1985) as well as in aphasics (Greenblatt, 1983; Seldon, 1985). With regard to pure alexics, Benson (1985) suggested that the ability to read ideograms is more impaired in pure alexics.

However, the studies from which the above generalizations were derived represent preliminary works on the issue of phonogram versus ideogram reading. The extent to which reliable conclusions are drawn from past studies is rather limited due to a flaw (or flaws) in test materials and/or data presentation. With regard to the test material, the stimulus words/letters were unspecified (Miura, 1933; Kotani, 1935; Ohashi, 1965; Sasanuma, 1974, 1975, 1980*a,b*, 1986; Yamadori, 1975, 1980, 1982; Hirose *et al.*, 1977; Kurachi *et al.*, 1979; Hayashi *et al.*, 1985; Iwata, 1985; Yamadori *et al.*, 1985; Kawahata *et al.*, 1988). In some others (Sasanuma and Fujimura, 1971; Sasanuma and Monoi, 1975; Torii *et al.*, 1976; Iwata *et al.*, 1979), the patients' reading abilities were tested with only 10 items. Nearly 2000 ideographic characters are in common use in the Japanese language, whereas there are only 46 basic phonograms. The performance of ideogram reading would depend partly on what scripts were employed, since many ideograms are difficult to read by less well-educated persons. Inclusion of uncommon ideograms in the stimulus set, such as in Torii *et al.* (1976), may lower the score for ideograms, making the overall performance pattern look as if phonograms and ideograms were dissociated in reading. Therefore, elementary ideographic stimuli must be chosen. Furthermore, which phonographic and ideographic materials were used must be clearly specified, and the number of test items should also be sufficiently large to permit a fair sampling of ideograms.

With respect to the manner of data presentation, the percentages of correct responses for individual cases were not provided (Miura, 1933; Kotani, 1935; Ohashi, 1965; Sasanuma, 1975; Yamadori, 1975, 1982; Hirose *et al.*, 1977; Kurachi *et al.*, 1979; Iwata, 1985), or the percentages of correct responses were presented only for patients as a group (Sasanuma and Fujimura, 1971). In another study (Sasanuma and Monoi, 1975), performance data were shown, but our statistical analysis of the data revealed an absence of any dissociation between phonograms and ideograms, contrary to the authors' assertion.

Given the inadequate experimental design of past studies, findings concerning phonogram-ideogram dissociations must be interpreted with caution. While a selective impairment of phonogram processing has been linked with aphasia (Sasanuma, 1975;

Yamadori, 1975), such a generalization needs to be carefully reassessed. Furthermore, because most of the past studies concerning phonogram-ideogram dissociations were single case studies (Miura, 1933; Kotani, 1935; Ohashi, 1965; Sasanuma, 1974, 1980*a*; Sasanuma and Monoi, 1975; Yamadori, 1975, 1980; Hirose *et al.*, 1977; Kurachi *et al.*, 1979; Iwata, 1985), inappropriate generalizations may have been made. Our clinical experience, however, has suggested that impairment patterns are not uniform among the patients of the same aphasia type, which is contrary to previous reports. In seeking a conclusion which is truly representative of a certain population, a large number of subjects within the population must be tested and possible differences of individual behaviour must be taken into account.

The issue of the phonogram-ideogram dissociation in Japanese aphasics and alexics has also been discussed in relation to the lesion site. For example, it is claimed that 'phonetic symbols and ideographs are localized to different regions of the cerebral cortex' (Mayeux and Kandel, 1991). Other researchers stated that damage to the more anterior portions of the left hemisphere interferes with phonogram reading, whereas more posterior lesions tend to impair the reading of ideograms (Benson, 1985) or both types of script (Moscovitch, 1979). Greenblatt (1983) also mentioned that phonogram reading is more severely disturbed than is ideogram reading when the lesion is angulotemporal or more diffusely peri-Sylvian.

Case studies which intended to identify the lesion site responsible for the phonogram-ideogram dissociation are abundant. According to such studies, reading of phonograms becomes more severely impaired with a lesion in the left angular gyrus (Yamadori, 1975; Iwata, 1985; Yamadori *et al.*, 1985), the left posterior middle temporal gyrus (Yamadori *et al.*, 1985), the left posterior inferior temporal lobe and the lateral occipital lobe (Kawahata *et al.*, 1988), or a subcortical lesion in the left superior temporal lobe and angular gyrus (Hayashi *et al.*, 1985). On the other hand, ideogram reading has been reported to be more impaired with damage to the left middle temporal gyrus (Mochizuki and Ohtomo, 1988), the left posterior middle temporal gyrus (Yamadori *et al.*, 1985), the left posterior inferior temporal lobe (Iwata, 1985; Kawahata *et al.*, 1988) or the left posterior inferior temporal gyrus and surrounding areas (Kawamura *et al.*, 1987).

In linking phonogram-ideogram dissociations with lesions sites, one should keep in mind that most of the above studies (Yamadori, 1975; Hayashi *et al.*, 1985; Iwata, 1985; Yamadori *et al.*, 1985; Kawahata *et al.*, 1988) are inadequate in the stimuli used and/or the manner of data presentation, as mentioned above. Furthermore, since all of the lesion studies are case reports, the conclusions are applicable only to the particular patients examined. It is difficult to make generalizations from past case studies with regard to the consequence of damage to the particular regions of the brain in aphasic-alexic patients.

The present study examines the ability of alexic and aphasic patients to perform oral reading of phonographic, ideographic and numerical scripts in a manner that meets the following conditions necessary to yield objective and unequivocal data: a sufficiently large number of specified stimulus materials, ideographic stimuli which are easy to read by any normal individuals, presentation of individual performance data and application of proper statistics and examination of several patients for each aphasia-alexia group. The goals of the present study are to answer the following questions: (i) can phonograms and ideograms be truly dissociated in oral reading? (ii) if such dissociations exist, is it linked with a particular aphasia-alexia type? (iii) is it linked with damage to a specific site of the brain?

METHODS

Subjects

The subjects comprised seven pure alexics (6 males and one female), 23 Broca aphasics (17 males and six females), 13 Wernicke aphasics (seven males and six females) and seven patients with alexia with agraphia (six males and one female). During the course of the study, two pure alexics, five Broca aphasics, three Wernicke aphasics and two alexic-agraphics were examined twice or three times. All of our cases were confirmed to be right-handed. The aetiology was either cerebral infarct or haemorrhage. They had at least an elementary school education and the age range of patients was 35–79 yrs. Informed consent was obtained from all the subjects who took part in this study.

Aphasia classification

Assessment of aphasia was performed with the fluency and severity ratings of the Boston Diagnostic Aphasia Examination (Goodglass and Kaplan, 1972), the shortened version of the Token Test (TT) (Spellacy and Spreen, 1969) and our aphasia test, which was employed at Mihara Memorial Hospital. Our test included the following subtests: examination of spontaneous speech; naming of 24 items; auditory comprehension of 24 object names and nine complex oral commands; repetition of six words and 10 sentences; reading comprehension of 12 words and four sentences; description of a picture by writing. Five sentences in the repetition task were taken from those used in the Japanese version of the Stanford-Binet test (Tanaka, 1954). The Broca and Wernicke aphasics were distinguished using the fluency rating scale employed by Goodglass and Kaplan (1972). The Broca aphasics had relatively good auditory comprehension skills, whereas comprehension was poor for the Wernicke aphasics. All of the Broca and Wernicke aphasics were impaired in sentence repetition, with accuracy rates no greater than 60%. The patients with alexia with agraphia demonstrated a deficit of reading and writing, with scores for sentence reading and writing no higher than 50% and 10%, respectively. In contrast, the speech and auditory comprehension of these patients were nearly normal. The pure alexics yielded scores below 50% in reading, and scores at least 80% in writing in phonograms, whereas the other skills were nearly unimpaired. Upon the auditory presentation of six words, all of the pure alexics were able to correctly point to the corresponding words written in phonograms and ideograms, a result suggesting their preserved ability to recognize phonograms and ideograms. Each patient was classified according to the results of the language examination independently of any lesion localization.

Computerized tomography (CT) scan localization of lesion

A set of CT images with and without contrast enhancement was obtained for each patient. The inclination of the gantry of the CT scans was adjusted to zero angle with the orbitomeatal line. The apparatus employed was either a Hitachi CT-H or Toshiba 60-A. The CT scans were obtained during the following periods after the onset of aphasia: from 2 d to 10 mths (mean, 2.7 mths) and from 1 d to 8 mths (mean, 2.5 mths) for the Broca aphasics with cerebral infarction and those with cerebral haemorrhage, respectively; from 4 d to 34 mths (mean, 9.3 mths) for the Wernicke aphasics with cerebral infarction, and at the seventh day for the Wernicke aphasic with cerebral haemorrhage; from 1 d to 20 mths (mean, 5.3 mths) and from 4 d to 4 mths (mean, 2.1 mths) for the patients with alexia with agraphia with cerebral infarction and those with cerebral haemorrhage, respectively; and from 10 d to 13 mths (mean, 2.9 mths) for the pure alexics, all of whom had suffered cerebral infarction.

The lesion localization was based on the atlases of Matsukawa *et al.* (1982) and Matsui and Hirano (1978), where the brain was cut in 1 cm thick sections with the plane of each section angled at zero degrees to the orbitomeatal line so as to duplicate the planes of the sections on the CT scans. The lesion sites were determined from the CT scans without knowledge of the aphasia type, and were plotted on idealized cross-sectional model drawings. Two of the authors independently made a drawing for each CT scan, and mutally agreed upon a single drawing whenever their drawings were discrepant with respect to site and extent of the lesion. Figure 1 shows a sample CT scan and a corresponding drawing on a template. In the set

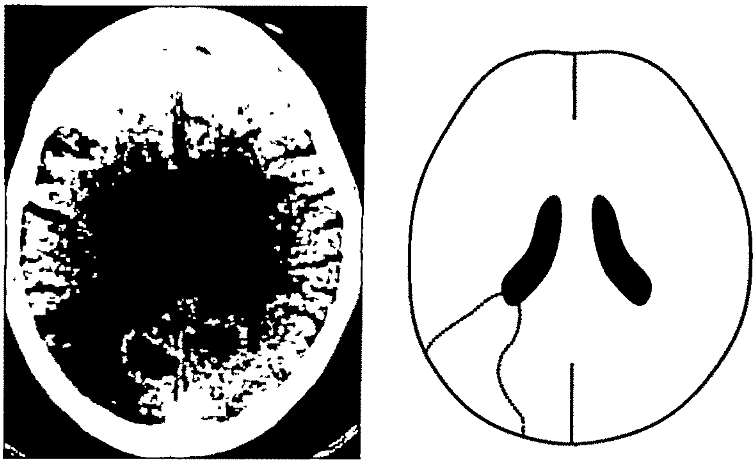

FIG. 1 A sample CT scan (*left*) and the lesion outlined on a template (*right*).

of four templates on which lesions were plotted (Figs 2, 3), the second lowest slice included the posterior half of the left inferior frontal gyrus (Broca's area) and the posterior half of the left superior temporal gyrus (Wernicke's area). The third to the lowest slice probably also included the Wernicke's area and the left angular gyrus. The highest slice involved the left angular gyrus.

Patients with multiple lesions were excluded. Only the patients who satisfy the following conditions were employed: for the Broca aphasics, the lesion was within the left frontal or fronto-parietal lobes, including their deep white matters; for the Wernicke aphasics, the lesion was within the left temporal lobe or temporo-parietal lobes including the temporo-occipital junction; for the pure alexics, the lesion was within the left occipital lobe including the left temporal base. Among the patients with alexia with agraphia, six subjects had the significant part of the lesion in the left parietal lobe. One patient with alexia with agraphia (Case 6) revealed a lesion in the posterior portion of the left inferior to middle temporal gyri, and another (Case 7), a lesion which extended from the left postero-inferior temporal lobe to the left parietal lobe. One Wernicke's case had a lesion which extended from the left temporal lobe to the left temporo-occipital junction area.

Reading material

The set of basic Japanese phonograms consists of 46 letters. There are two types of Japanese phonograms (Kana), termed Hiragana and Katakana, of which the former is the more commonly used. As phonographic stimuli, all of the 46 basic Hiragana letters were employed.

As stated previously, the number of ideograms in common use is nearly 2000, and is therefore far greater than the number of phonograms. If all of the ideograms as well as the phonograms were employed to test reading accuracy, a situation would arise in which reading in ideograms was certainly more difficult than reading in phonograms, because the set of ideograms contains scripts that are unfamiliar to individuals with an education only to primary school level. In order to make a reasonable comparison, we selected a total of 46 ideograms (Table 1).

Some of the past studies used phonographic and ideographic words consisting of multiple scripts (e.g. Torii *et al.*, 1976; Sasanuma, 1986). We employed single-script stimuli for the following reasons. Single-letter ideographic words are more elementary and taught in earlier stages of education than compound ideographic words, i.e. words composed of two or more ideograms combined. In fact, of the 151 ideograms taught during the first 2 yrs in the elementary school, all except two represent common nouns by themselves. Therefore, we restricted our ideographic word to those which are taught during the first 2 yrs in elementary school, all of which represent common single-letter words. We also limited our phonographic stimuli to single phonograms in order to match the length of stimuli. This procedure eliminated the possibility that different lengths of phonographic and ideographic stimuli may confound results.

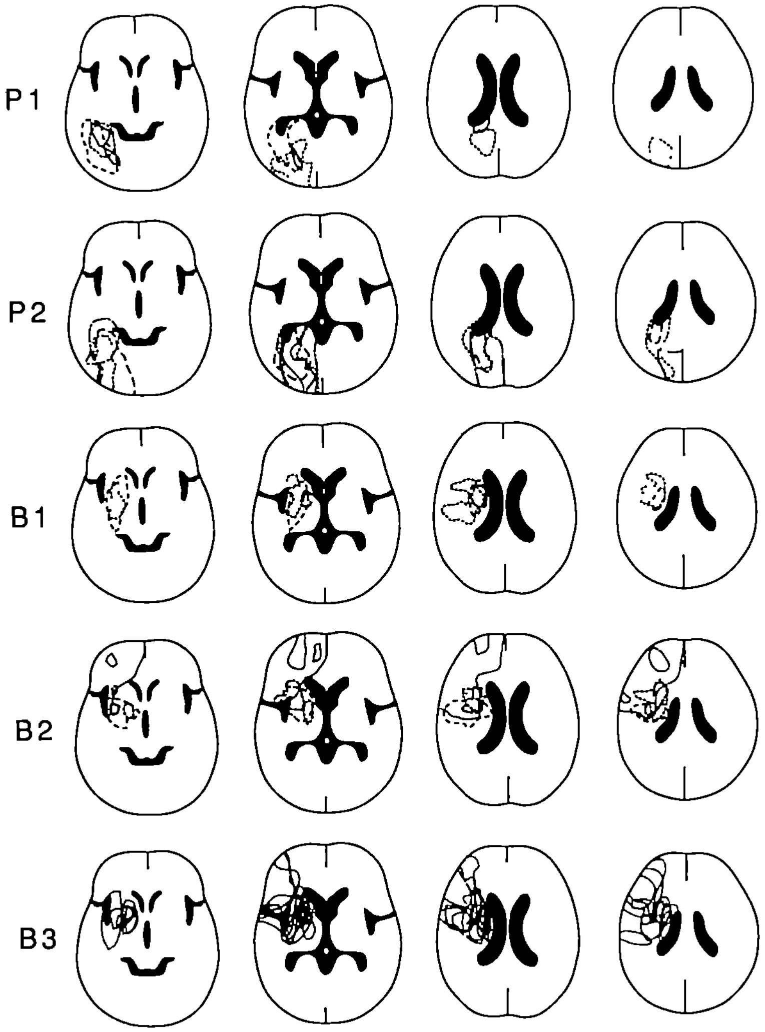

FIG. 2. Outlines of the lesions for each of the subgroups of patients defined on the basis of aphasia type and the patterns of impairment for phonograms and ideograms. P1 = pure alexics with a more severe impairment of ideogram reading; P2 = pure alexics in whom phonograms and ideograms were impaired to similar extents; B1 = Broca aphasics with a more severe impairment of ideogram reading; B2 = Broca aphasics with a more severe impairment of phonogram reading, B3 = Broca aphasics in whom phonograms and ideograms were impaired to similar extents.

The details of the procedure of ideogram selection were as follows: eighteen ideograms which were taught commonly during the first grade, and published in the second edition of the national textbook (used from 1910 to 1917), and in subsequent editions through to the fifth (used from 1940 to 1945) were the first selected. Then from among the 77 ideograms which were introduced during the first two grades in the above textbooks, 28 additional ideograms were selected randomly. The ideograms chosen in this manner were presumed to be among the easiest ones for the subjects since they were those taught to them during the initial period of their school life. It was also confirmed that most of these ideograms are still taught during the first 2 yrs under the current educational system. Furthermore, all of the ideograms chosen are

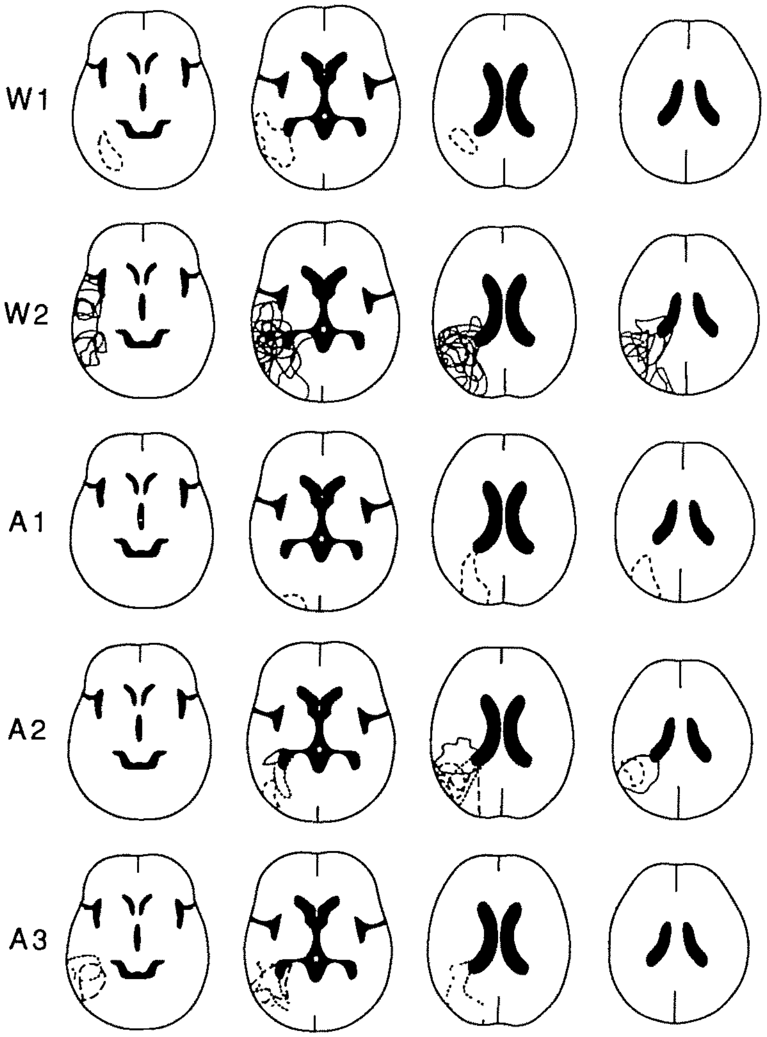

FIG. 3. Outlines of the lesions for each of the subgroups of patients defined on the basis of aphasia type and the patterns of impairment for phonograms and ideograms. W1 = a Wernicke aphasic with a more severe impairment of ideogram reading; W2 = Wernicke aphasics in whom phonograms and ideograms were impaired to similar extents; A1 = a patient with alexia with agraphia (AA) with an angular gyrus lesion exhibiting a more severe impairment of phonogram reading; A2 = patients with AA with angular gyrus lesions in whom phonograms and ideograms were impaired to similar extents, A3 = patients with AA with inferior temporal gyrus lesions.

among the 6000 basic Japanese words specified by the National Language Research Institute (1984), and all except one are among the most common 2000 words of the above 6000. These ideographic scripts are associated with clear meanings, and qualify as typical ideograms, unlike some less common ideograms which have little semantic value to most people.

Ten arabic numerals, from 0 to 9, were also included in the stimulus set to allow a broader comparison of results with those reported previously for other languages. All of the phonograms, ideograms and numerals were printed (each sized 2 cm in height×2 cm in width) in a random order for presentation.

TABLE 1 PHONOGRAPHIC (A) AND IDEOGRAPHIC (B) STIMULI USED IN THE READING TASK

A

あ	い	う	え	お	か	き	く	け	こ
さ	し	す	せ	そ	た	ち	つ	て	と
な	に	ぬ	ね	の	は	ひ	ふ	へ	ほ
ま	み	む	め	も	や	ゆ	よ	ら	り
る	れ	ろ	わ	を	ん				

B

人	山	小	大	口	下	女	子	土	上
川	火	月	水	日	中	木	手	牛	犬
毛	本	石	左	右	白	目	生	耳	竹
色	光	米	足	花	赤	麦	村	青	雨
夜	風	雪	鳥	雲	朝				

Procedures

Each stimulus letter was presented to the subject for a maximum of 15 s, during which time the patient was instructed to read the script aloud. The subject's hands were held immobile during the stimulus presentation so that manual tracing of the script could not facilitate reading performance through kinaesthetic cues.

All of the past studies concerned phonogram and ideogram reading tested patients' oral reading skills; many of the studies drew conclusions from the results of the oral reading tasks alone (e.g. Kurachi *et al.*, 1979; Yamadori, 1982; Iwata, 1985; Kawamura *et al.*, 1987; Mochizuki and Ohtomo, 1988). The purpose of our study was to reassess past conclusions and generalizations made in this salient aspect of reading.

RESULTS

Our findings are presented as comparisons between phonograms, ideograms and numerals for the different aphasia types, and the relevant CT data are summarized in each case.

Pure alexia

Phonograms versus ideograms. Table 2 shows the percentages of correct responses for the 46 phonograms, 46 ideograms and 10 numerals in the seven subjects. Since two subjects were tested more than once, we obtained a total of 11 data sets, which are presented according to their rank ordering based on the accuracies for ideograms. Examination of the individual data indicated that the oral reading of phonograms was significantly better than that of ideograms in one case (Case 5) among the five subjects tested once only ($P < 0.005$: Fisher's exact method, two-tailed. This was also used

TABLE 2 CASE DESCRIPTIONS AND THE PERCENTAGES OF CORRECT RESPONSES FOR EACH PURE ALEXIC PATIENT AT EACH TESTING SESSION

Case	*Sex*	*Age (yrs)*	*Aetiology*	*Post-onset time (mths)*	*Phonograms*	*Ideograms*	*Numerals*	*Ideograms (<6 strokes)*	*Ideograms (6–12 strokes)*
3	M	75	I	0	91.3	93.5	100	96.4	88.9
1, test 2	M	59	I	19	89.1	82.6	80	82.1	83.3
1, test 3	M	60	I	24	87.0	80.4	70	88.9	72.2
7	M	62	I	18	73.9	73.9	100	75.0	72.2
1, test 1	M	58	I	5	93.5 >**	68.9	80	85.2 >**	44.4
4	F	69	I	3	78.3	63.0	60	60.7	66.7
2, test 3	M	54	I	3	89.1 >**	54.3	100	67.9 >*	33.3
2, test 2	M	54	I	2	67.4	52.2	90	60.7	38.9
5	M	54	I	0	80.4 >**	32.6	80	42.9	16.7
2, test 1	M	53	I	1	19.6	10.9	70	17.9	0
6	M	72	I	14	0	8.7	40	17.9	5.6

I = ischaemic. Direction and significance level for the difference, if any, between the scores for phonograms and ideograms, and between the scores for ideograms of >6 strokes and ideograms of 6–12 strokes are also indicated ($^{*}P < 0.05$; $^{**}P < 0.01$).

hereafter in testing differences between performance levels). In the remaining four cases, the differences were not significant. Concerning the two pure alexics examined more than once, each individual revealed a phonogram-ideogram dissociation on only one occasion (Case 1, test 1; Case 2, test 3). There were no cases in which the scores for ideograms were significantly better than those for phonograms.

Ideograms of high versus low complexity. When the performance levels for phonograms and ideograms are different, one possible factor contributing to the discrepancy could be the different visuospatial or configurational complexities of the two types of stimuli. For measuring the complexity of Japanese phonograms, the index called the 'number of strokes' (Kabashima and Satake, 1973) has been proposed. All the basic phonograms are formed with not more than five strokes according to the method. For Japanese ideograms, the number of strokes is also a standard measure representing their graphic complexity. Since the ideograms employed here ranged from 2 to 12 in their number of strokes, some of the ideograms can be considered as graphically more complex than the phonograms. In order to assess the possible effects of visuospatial complexity on reading performance, the ideograms were classified into two subgroups: a high complexity group composed of those formed with strokes ranging in number from 6 to 12, and a low complexity group composed of those written with 2 to 5 strokes (<6 strokes). The high complexity group comprised 28 scripts, and the low complexity group, 18 scripts.

Comparisons of the scores for the high and low complexity stimuli revealed that the accuracy for low complexity ideograms was significantly higher than that for high complexity ideograms in two cases (Case 1, test 1, $P < 0.01$; Case 2, test 3, $P < 0.05$). These two cases were also included among the three cases in which phonogram reading was significantly better than ideogram reading. When the accuracies for only the low complexity ideograms were compared with those for phonograms, it was found that the significance of the phonogram-ideogram differences present in the previous analysis based on the total set of ideograms disappeared for the above two cases. In one other subject (Case 5), however, the reading performance for low complexity ideograms was still significantly poorer than that for phonograms even when the configurational complexities were controlled. This case was in the acute phase (11 d post-onset), and the unique performance pattern could have been related to the distinctive anatomical condition, in which tissue swelling affected regions other than the lesion site.

Numerals. Comparisons of the accuracy levels for numerals with those for phonograms and ideograms demonstrated that the reading ability of numerals was relatively well maintained even when the oral reading of non-numerical scripts was impaired. In one (Case 2, test 1) of the two cases in which only less than 20% of the phonograms and ideograms were read correctly, numerals were read with a significantly higher accuracy ($P < 0.05$) than both phonograms and ideograms. In the other case (Case 6) of the two, numeral reading was better than only one phonogram reading ($P < 0.01$). Numerals were read more correctly than only ideograms ($P < 0.01$) in two cases (Case 2, test 3; Case 5).

Since the complexity of configuration was found to affect the reading performance of pure alexics, it could be argued that the lower scores for phonograms and ideograms than those for numerals resulted from the visuospatial complexity of the non-numerals used. The data were, therefore, re-examined by selecting only the responses to 10 ideograms written with not more than three strokes and 10 phonograms with one or two strokes in order to match the stimuli in terms of graphic complexity. It was found that the score for numerals was still significantly higher than that for the ideograms in one case (Case 2, test 1) ($P < 0.05$). On the other hand, the reading of numerals was no longer statistically worse than that for the phonograms.

Computerized tomography findings. Figure 2 (P1 and P2) illustrates the lesions sites for two subgroups of pure alexic patients, i.e. those who showed phonogram-ideogram dissociation and those who did not, in an attempt to identify possible anatomical structures which might determine reading behaviour. There appeared, however, to be no such critical structures: the parts which were commonly damaged among one group of patients overlapped with those commonly damaged among the other group of patients. Similarly, no specific anatomical structures were found which could differentiate subgroups of patients defined on the basis of the performance in numeral reading. The one subject (Case 5) who exhibited a more severe disturbance for ideograms than for phonograms, even with the materials controlled in graphic complexity, was not distinguishable from the other cases in terms of the lesion site. He was in the acute phase (11 d post-onset), and his performance may have been related to this distinctive physiological condition.

Broca aphasia

Phonograms versus ideograms. Table 3 shows the percentages of correct responses for phonograms, ideograms and numerals in the 23 patients according to the rank ordering of performance level for ideograms. Five cases were tested more than once. Comparisons of the data for phonograms and ideograms indicated that there was no consistency regarding which type of scripts was better read among the Broca aphasics. In four cases (Case 3, test 2; Case 4, test 2; Cases 8, 23), the performance level for ideograms was significantly higher than that for phonograms ($P < 0.01$), but on the other hand, three cases showed a significantly better performance for phonograms (Case 20, $P < 0.01$; Cases 10, 16, $P < 0.05$). In the other 16 cases, the scores were similar, or the differences were not significant, for the two types of scripts.

TABLE 3. CASE DESCRIPTIONS AND THE PERCENTAGES OF CORRECT RESPONSES FOR EACH BROCA APHASIC PATIENT AT EACH TESTING SESSION

Case	*Sex*	*Age (yrs)*	*Aetiology*	*Post-onset time (mths)*	*Phonograms*	*Ideograms*	*Numerals*	*Ideograms (<6 strokes)*	*Ideograms (6–12 strokes)*
15	M	59	I	10	100.0	100.0	100	100.0	100.0
1, test 1	F	49	H	45	95.7	97.8	100	96.4	100.0
23	F	40	H	3	78.3 <**	97.8	100	96.3	100.0
18	M	44	I	2	100.0	97.8	100	96.4	100.0
13	M	50	H	29	100.0	97.8	100	100.0	94.4
1, test 2	F	50	H	48	95.7	95.7	100	92.9	100.0
21	M	62	I	2	95.7	95.7	90	100.0	88.9
2, test 2	M	46	I	7	84.8	91.3	80	85.7	100.0
22	M	57	I	3	95.7	91.3	100	89.3	94.4
19	M	45	I	5	89.1	87.0	100	89.3	83.3
3, test 2	M	52	I	28	50.0 <**	87.0	90	82.1	94.4
10	F	45	I	1	100.0 >*	84.8	100	82.1	88.9
6	F	71	I	1	89.1	80.4	90	82.1	77.8
4, test 2	M	56	I	9	47.8 <**	80.4	70	75.0	88.9
5, test 3	M	54	I	23	71.7	80.4	100	82.1	77.8
2, test 1	M	46	I	6	84.8	78.3	100	64.3 <**	100.0
7	M	50	H	11	82.6	76.1	100	78.6	72.2
9	M	38	H	2	84.8	75.6	100	77.8	72.2
11	M	48	I	4	67.4	75.6	80	70.4	83.3
8	F	38	I	3	26.1 <**	73.9	100	82.1	61.1
20	M	57	H	10	93.5 >**	67.4	100	60.7	77.8
14	M	63	I	4	60.9	64.4	90	70.4	55.6
4, test 1	M	55	I	2	37.0	52.2	40	35.7 <*	77.8
5, test 1	M	52	I	8	52.2	52.2	70	57.1	44.4
5, test 2	M	52	I	9	65.2	44.4	40	35.7	55.6
3, test 1	M	51	I	11	26.1	41.3	70	42.9	38.9
12	F	42	H	4	19.6	39.1	80	39.3	38.9
17	M	71	I	1	28.3	39.1	40	42.9	33.3
16	M	63	I	2	23.9 >*	6.5	30	10.7	0

I = ischaemic; H = haemorrhagic. Direction and significance level for the difference, if any, between the scores for phonograms and ideograms, and between the scores for ideograms of <6 strokes and ideograms of 6–12 strokes are also indicated (*$P < 0.05$; **$P < 0.01$).

Ideograms of high versus low complexity. There were two Broca aphasic cases (Case 2, test 1; Case 4, test 1) in which the differences between the scores for the less complex and more complex materials were significant ($P < 0.05$). However, in contrast to the trend observed in the pure alexia group, the effects of visuospatial complexity on the reading of ideograms were qualitatively distinct; i.e. the high complexity scripts were read more accurately than the low complexity scripts by these two aphasics. In the other 21 cases, the scores for the low and high complexity stimuli were not significantly different.

Another finding was that the configurational complexity of the stimuli did not systematically contribute to the differences in scores for phonograms and ideograms. Even when the ideographic stimuli were limited to those of the low complexity group in order to match the phonograms and ideograms for their visuospatial complexity, three cases still yielded scores for ideograms which were significantly higher than those for phonograms in this comparison (Case 8, $P < 0.01$; Case 3, test 2, Case 4, test 2, $P < 0.05$). In two cases, on the other hand, the accuracies for ideograms were significantly lower than those for phonograms (Case 10, $P < 0.01$; Case 5, test 2, $P < 0.05$). Taken together, the above results suggest that the differences between the performances for phonograms and ideograms cannot be simply ascribed to differences in visuospatial complexity. Furthermore, variations among the subjects in terms of the influence of the script-type on the reading performance, i.e. whereby phonograms were found to be more difficult than ideograms by some subjects but the opposite pattern held true for some others, were confirmed with this more strictly matched set of stimuli.

Numerals. There was one case (Case 12) in which the accuracy of numeral reading was significantly higher than those of both phonogram reading and ideogram reading ($P < 0.05$). In two other patients, reading of numerals was significantly better than only that of phonograms (Case 8, $P < 0.01$; Case 3, test 1, Case 3, test 2, $P < 0.05$). These findings imply that the reading performance for numerals was more closely correlated with that for ideograms, rather than phonograms. The Pearson product-moment correlation coefficients ($r = 0.80$, between numerals and ideograms; and 0.68, between numerals and phonograms) supported this observation, but the difference in value between the two coefficients was non-significant.

The data were next re-examined using the above-mentioned 10 graphically simple phonograms and 10 simple ideograms in order to control the visuospatial complexity of the stimuli. The results obtained indicated that numerals were still more accurately read than both phonograms and ideograms in one case (Case 12), and than only phonograms in one case (Case 8) $P < 0.05$). Thus, graphic complexity did not appear to be the only factor causing the performance differences in these subjects.

Computerized tomography findings. Figure 2 (B1–B3) illustrates the lesion sites for each of three subgroups of Broca aphasics defined on the basis of the patterns of impairment of the two types of scripts; namely, superior reading of phonograms, superior reading of ideograms and non-differential reading of phonograms and ideograms. The lesion sites in these three subgroups overlapped to a considerable extent. Furthermore, lesions at similar sites were found to yield various patterns of phonogram and ideogram disturbance among the patients. The only case (Case 12) who read numerals significantly better than either phonograms or ideograms was also uncharacteristic as regards lesion site. It may also be added that examination of the cases with infarction or of haemorrhage only failed to identify any distinct anatomical structures which might be considered critical in causing a specific phonogram-ideogram dissociation pattern.

Wernicke aphasia

Phonograms versus ideograms. Table 4 shows the percentages of correct responses for phonograms, ideograms and numerals in the 13 patients according to the rank ordering of performance level for ideograms. Three cases were tested twice. It was found that ideogram reading was significantly more impaired than phonogram reading ($P < 0.05$) in only one case (Case 2, test 1). In the remaining 12 cases, there were no significant differences between the scores for phonograms and ideograms.

Ideograms of high versus low complexity. Statistical analysis of the data demonstrated that the performances for ideograms taken from the high complexity group and those from the low complexity group were not significantly different. Effects of visuospatial complexity did not appear to be significant in this group.

TABLE 4. CASE DESCRIPTIONS AND THE PERCENTAGES OF CORRECT RESPONSES FOR EACH WERNICKE APHASIC PATIENT AT EACH TESTING SESSION

Case	*Sex*	*Age (yrs)*	*Aetiology*	*Post-onset time (mths)*	*Phonograms*	*Ideograms*	*Numerals*	*Ideograms (<6 strokes)*	*Ideograms (6–12 strokes)*
12	F	60	I	1	100.0	100.0	100	100.0	100.0
8	F	60	I	1	95.7	95.7	100	96.4	94.4
3, test 2	M	60	I	30	89.1	95.7	100	96.4	94.4
10	F	71	I	0	100.0	95.7	100	96.4	94.4
6	M	76	I	20	87.0	95.7	100	92.9	100.0
4	M	69	I	28	84.8	91.3	100	92.9	88.9
13	M	48	H	2	76.1	91.3	70	96.4	83.3
3, test 1	M	59	I	12	73.9	89.1	100	96.4	77.8
5	F	68	I	2	97.8	84.8	100	89.3	77.8
7	F	71	I	34	80.4	82.6	60	78.6	88.9
1, test 2	M	74	I	4	54.3	56.5	50	42.9	77.8
9	M	60	I	2	67.4	56.5	90	64.3	44.4
11	F	71	I	4	26.1	32.6	30	42.9	16.7
2, test 2	M	66	I	23	23.9	20.0	60	25.0	11.1
1, test 1	M	74	I	1	6.5	19.6	30	21.4	16.7
2, test 1	M	66	I	21	26.1 >*	6.5	60	10.7	0

I = ischaemic; H = haemorrhagic. Direction and significance level for the difference, if any, between the scores for phonograms and ideograms, and between the scores for ideograms of <6 strokes and ideograms of 6–12 strokes are also indicated (*$P < 0.05$, **$P < 0.01$)

The accuracies for phonograms were compared with those for low complexity ideograms in order to match the stimuli for visuospatial complexity. In this comparison, ideograms were read significantly more accurately than phonograms ($P < 0.05$) in two cases (Case 3, test 1; Case 13). It should be added, however, that these cases had not exhibited significant discrepancies between their scores for phonograms and ideograms in the above-mentioned analysis of the total set.

Numerals. The accuracy levels for numerals were significantly higher than those for ideograms in one case on two different occasions (Case 2, test 1, $P < 0.01$; Case 2, test 2, $P < 0.05$). Even when the visuospatial complexities of the stimuli were controlled by limiting the ideographic stimuli to the 10 scripts with two or three strokes, the discrepancy in scores obtained by this case on one occasion (Case 2, test 2) for the numerals and ideograms remained significant ($P < 0.05$). No significant differences existed between the scores for phonograms and numerals in any of the subjects.

Computerized tomography findings. An examination of the patients' lesion sites (Fig. 3, W1 and W2) indicated that the case (Case 2) exhibiting a more severe impairment of ideograms was distinguishable from the other cases on the basis of having the lesion in the lowest plane. The lesion in this case, unlike those of the others, appeared to involve the temporo-occipital junction or the occipital periventricular area. As regards the two cases (Cases 3, 13) which showed a more severe impairment of phonograms when tested with phonograms and graphically simple ideograms, their lesions were found to be uncharacteristic.

Alexia with agraphia

Phonograms versus ideograms. Table 5 shows the percentages of correct responses for phonograms, ideograms and numerals in the seven patients according to the rank ordering of performance level for ideograms. Two cases (Cases 6, 7) had lesions which

TABLE 5 CASE DESCRIPTIONS AND THE PERCENTAGES OF CORRECT RESPONSES FOR EACH PATIENT WITH ALEXIA WITH AGRAPHIA AT EACH TESTING SESSION

Case	*Sex*	*Age (yrs)*	*Aetiology*	*Post-onset time (mths)*	*Phonograms*	*Ideograms*	*Numerals*	*Ideograms (<6 strokes)*	*Ideograms (6–12 strokes)*
2	M	66	H	72	97.8	100.0	100	100.0	100.0
1, test 2	F	55	I	1	97.8	100.0	100	100.0	100.0
3	M	35	H	1	84.8	97.8	100	96.4	100.0
1, test 1	F	55	I	0	78.3	93.5	90	85.7	100.0
4	M	64	I	2	76.1 <*	93.5	100	92.9	94.4
7	M	64	I	2	95.7	93.5	100	96.4	88.9
5	M	57	I	4	97.8	93.5	80	92.9	94.4
6, test 2	M	79	I	3	95.7	84.8	100	89.3	77.8
6, test 1	M	79	I	1	65.2	52.2	90	60.7	38.9

I = ischaemic; H = haemorrhagic Direction and significance level for the difference, if any, between the scores for phonograms and ideograms, and between the scores for ideograms of <6 strokes and ideograms of 6–12 strokes are also indicated (*$P < 0.05$).

involved the posterior portion of the left inferior to middle temporal gyri. The lesion was found to be confined to this area in Case 6, but that of the other case (Case 7) extended from the posterior part of the inferior temporal gyrus to possibly the white matter underlying the angular gyrus. All of the remaining cases (Cases 1–5) had lesions in the angular gyrus or in the periventricular area of the parietal lobe. The middle or inferior temporal gyrus of their underlying white matter may also be involved in Cases 1, 2, 3. The reading of ideograms was significantly better than that of phonograms in one case (Case 4) ($P < 0.05$), but no significant differences were noted between the scores for the two types of scripts in the other six cases.

Ideograms of high versus low complexity. Examinations of the data indicated that the performance level for the graphically more complex ideograms was not significantly different from that for the less complex stimuli in any subject. Comparisons between the accurancies for phonograms and ideograms with the stimuli matched for graphic complexity demonstrated no significant difference in any case. While the significantly better reading of ideograms found in the total set of phonograms and ideograms in Case 4 became non-significant, the accuracy level for the low complexity ideograms was similar to that for the low complexity and high complexity ideograms combined. It seems likely therefore that the smaller sample size of the lower complexity materials gave rise to the loss of significance in this case.

Numerals. There were no significant differences between the performance levels for numerals and ideograms or between the accuracies for numerals and phonograms.

Computerized tomography findings. Rows A1 and A2 of Fig. 3 illustrate the lesion sites for two subgroups of patients with alexia with agraphia defined on the basis of the patterns of impairment. All of the cases thus represented had damage to the left angular gyrus or the periventricular area of the parietal lobe. The patient (Case 4) exhibiting superior reading of ideograms appeared to have a more extensive lesion, reaching the left occipital lobe, than did the other cases. Row A3 of Fig. 3 shows the lesion sites of the two patients with damage to the posterior part of the left inferior temporal gyrus. Among them, one case (Case 7) had a lesion which extended from the posterior part of the left inferior temporal gyrus to possibly the white matter underlying the left angular gyrus, whereas the lesion in the other case (Case 6) was primarily in the posterior portion of the left inferior to middle temporal gyri.

DISCUSSION

Two principal reasons lay behind the present study. The first one was that our clinical observations frequently failed to coincide with the generalizations on reading performance in Japanese alexics and aphasics reported in widely accepted handbooks and textbooks. The inference of this literature is that a specific aphasia type or lesion site is associated with a particular impairment pattern of phonogram and ideogram reading. The second reason was the unsatisfactory research design of the earlier studies from which such generalizations were drawn. The weaknesses in experimental design of the past studies include: (i) unspecified or inappropriate test stimuli and an insufficient number of stimuli; (ii) the absence of individual performance data to support conclusions; (iii) generalizations were sometimes based on single cases. In the present study the experiments were designed to avoid such problems in order to resolve the phonogram-ideogram problem unequivocally.

In an extensive review of past studies (Paradis *et al.*, 1985), assessment of the adequacy of the experimental design was not included. Our results are discussed below in comparison with those of the past studies taking this into account.

Phonograms versus ideograms

Pure alexia. The present study revealed that the following two types of impairment were found among the pure alexics: (i) impairment of phonograms and ideograms to similar degrees; (ii) more severe impairment of ideograms than of phonograms. In no cases were ideograms read significantly better than phonograms. There have been case studies of Japanese pure alexics (e.g. Miura, 1933; Sasanuma, 1974; Hirose *et al.*, 1977; Kurachi *et al.*, 1979; Yamadori, 1980), but in these studies the conclusion of whether or not a patient was more disabled in reading one type of script than the other was obscure because of the absence of the patients' performance data. The present investigation clearly showed that Japanese pure alexic patients are either equally disturbed in phonogram and ideogram reading or more impaired in ideogram reading. Our data, however, do not exclude the possibility that phonogram reading can be more disturbed in pure alexia. Additional research may reveal the presence of such an impairment pattern in pure alexics.

Many Japanese ideograms are more complex than phonograms in their configuration, and it may be assumed therefore that the greater visuospatial complexity of some ideograms is one factor contributing to the poorer performance of ideogram reading. This hypothesis was supported in two of the three cases in which ideograms were significantly more impaired than phonograms. In the other case, however, the reading performance for ideograms was poorer even with visuospatially simpler ideographic stimuli.

The role of visuospatial complexity of stimuli in reading does not appear to have been fully investigated in Western languages. It has been mentioned that simply designed letters may be recognized more readily than more complex letters (Benson and Geschwind, 1969). However, an extensive study of the effects of graphic complexity on reading is probably hindered by the nature of the alphabetical system, which consists of letters which are fairly even in their graphic complexity. The use of Japanese ideograms, as in the present study, may help to shed more light on the nature of pure alexia since ideograms include graphically simple scripts as well as complex ones. Our results indicate that stimuli written with many strokes may be read more erroneously in some pure alexics. Our findings lend support to the idea that the graphic complexity of Japanese ideograms is one possible factor affecting the reading performance of pure alexics (Hatano *et al.*, 1986). Nevertheless, it should be stressed that substantial individual differences exist in the degree to which the graphic complexity may affect reading. In only two of the present seven patients were the graphically simpler ideograms read significantly better than the more complex ones.

It has been proposed that pure alexia occurs when the following two anatomical conditions coexist: right hemianopsia due to a lesion in the left occipital lobe, and a lesion in the pathway carrying the visual information from the right to the left hemisphere; namely, the splenium of the corpus callosum, or the callosal fibres from the splenium in the left hemisphere. The former condition allows only the right hemisphere to receive the visual input, whereas the latter condition disrupts the transfer of visual information from the right occipital lobe to the area of the left hemisphere responsible for decoding printed letters. Pure alexia is the result of a disconnection between the visual cortex of the occipital lobes and the language-dominant left hemisphere. Our CT findings for the patients examined in this study are consistent with this theory.

According to Sugishita *et al.* (1978, 1986), a section of the posterior callosum including the splenium tends to cause more severe impairment of the reading of phonograms than of ideograms presented tachistoscopically to the left hemifield in Japanese hemialexic patients. Furthermore, ideograms were responded to more correctly than were phonograms in interhemifield same-different judgement tasks (Sugishita *et al.*, 1986). They hypothesized that transfer from the right hemisphere to the left may occur more efficiently for ideograms than for phonograms because ideograms are generally more distinct from each other in their configuration, and are less readily confused with one another (Tanaka, 1977). We also speculate that ideograms, which are more strongly associated with concepts, may provoke greater neuronal activities in reading than do phonograms even in the right hemisphere, and that such neuronal activation somehow facilitates the interhemispheric transfer of visual information from the right hemisphere to the left.

The above results and ideas concerning hemialexics may appear to contradict our finding that reading of ideograms was sometimes more impaired in pure alexia. We hypothesize, therefore, that the impairment of reading of more graphically complex scripts observed in two pure alexics did not originate in the lesion of the callosal fibres itself, but rather, in the lesion of the left occipito-temporal lobe other than the callosal fibres. It was not possible, however, to identify from our CT findings any specific anatomical structures in the occipito-temporal lobe which may have caused the difficulty in the reading of more complex scripts in the two patients. Effects of damage to a particular region may vary from one case to another. Furthermore, since each of the two cases exhibited significantly greater reading deficits of complex letters on only one of the three occasions of data collection, it can be concluded that the pattern of impairment resulted from the interaction between the lesion and the length of period after onset.

There was one case in which ideograms were more severely impaired than phonograms even when the two types of scripts with similar visuospatial complexities were presented.

This case was in the acute phase (11 d post-onset), and it is speculated that his unique performance pattern derived from his distinctive physiological condition, under which brain structures other than the lesion site were also likely to be affected. Detailed research on additional pure alexics in the acute as well as chronic stages needs to be conducted in order to confirm the precise effects of the post-onset period and possible individual variations occurring within the population.

Broca and Wernicke aphasias

In the present study, it became evident that no general and consistent patterns of reading performance were present among Broca aphasics. More specifically, the effects of the phonogram-ideogram distinction on reading performance were variable, and there were two conflicting directions of dissociation between phonograms and ideograms. Furthermore, a majority of the cases exhibited no dissociation between the two types of scripts.

Past studies of Broca aphasics reported phonogram-ideogram dissociations in only one direction, i.e. either phonogram reading or ideogram reading is significantly disturbed (Hirose, 1942; Torii *et al.*, 1976; Sasanuma, 1980*a*, 1986). However, the results of such studies, except that of Hirose (1942), do not appear reliable enough due to the unspecified test material (Sasanuma, 1980*a*, 1986) and the insufficient size of the stimulus set (Torii *et al.*, 1976). In view of our data showing that a variety of patterns of phonogram-ideogram disturbances coexists in Broca aphasics, Sasanuma's (1975) conclusion that phonograms tend to be more impaired than ideograms in Broca aphasia is evidently unsupportable.

It should also be stressed that the performance characteristics correlated neither with the lesions sites nor the length of the period post-onset. The lesions not only overlapped with each other between the subgroups of patients defined on the basis of reading impairment patterns, but also lesions at similar sites yielded various patterns of disturbance. No anatomical structures appeared to be critical in causing a specific pattern of reading deficit for phonograms and ideograms.

Besides the phonogram-ideogram distinction, the visuospatial complexity of stimuli was another variable for which individual differences within the group were evident. Two Broca aphasic cases read the graphically more complex scripts significantly better than they read the simpler ones. This finding was contrary to the tendency observed in pure alexia, i.e. two pure alexics were significantly more capable of reading graphically simpler ideograms than more complex ones. This discrepancy between aphasia and pure alexia could be accounted for anatomically. As we hypothesized previously, a lesion in the left occipito-temporal lobe may tend to disrupt the transfer of more complex visual information in pure alexia. However, both graphically simpler scripts and more complex ones should be processed equally well in the subjects with no left occipito-temporal lesions, such as the patients with Broca's aphasia. It is speculated that graphic complexity somehow increases the configurational distinctness of certain ideograms, which facilitates recognition of the scripts in some aphasic patients.

Concerning the Wernicke aphasics, all the cases, except one, showed no differential reading performance for phonograms and ideograms. In the one exceptional case, ideogram reading was significantly more disturbed. More severe disruption of phonogram reading, an impairment pattern which our patients did not demonstrate, has been reported to be evident in one Wernicke aphasic (Sasanuma, 1980*b*). The stimulus items used to test this patient were unspecified, but were at least indicated to be words composed of multiple scripts. The words written with phonograms require, with rare exceptions, greater numbers of scripts than do the same words written with ideograms. It is therefore possible that a greater difficulty reading longer phonographic words may have caused the more severe impairment of phonogram reading in Sasanuma's (1980*b*) case. Further research in Wernicke aphasia is needed to clarify whether the reading of single phonograms can be more impaired than the reading of single ideograms.

The case (Case 2) that exhibited the most severe impairment of ideograms was anatomically distinguishable from the others. The lesion in this case, unlike those of the others, appeared to involve the temporo-occipital junction or the occipital periventricular area. Although it could be speculated that damage to this area is responsible for the greater disturbance of ideograms, this Wernicke aphasic when observed on another occasion failed to exhibit a phonogram-ideogram dissocation. The effects of damage to this anatomical structure may thus vary as a function of the post-onset time length. Additional data are needed to verify this speculation. As regards the two patients (Cases 3, 13) who showed a more severe impairment of phonograms when tested with phonograms and ideograms matched in the graphic complexity, it cannot be explained anatomically what mechanism contributed to their performance.

The results for the Wernicke aphasics were not entirely identical to those for the Broca aphasics. The patterns of impairment among the Broca aphasics were more variable than those among the Wernicke aphasics. More specifically, none of the Wernicke aphasics showed a more severe disturbance of phonogram reading, whereas four Broca aphasics did so. Similarly, the percentage of cases exhibiting a phonogram-ideogram dissociation in the Broca aphasic group tended to be greater than that in the Wernicke aphasic group. Further investigations are needed to determine whether the discrepancies in these two aspects reflect a qualitative difference between the two types of aphasia.

Alexia with agraphia

The present results for the cases with an angular gyrus lesion suggested similar degrees of impairment for both phonograms and ideograms in every case except one. This exceptional case demonstrated a more severe deficit of phonogram reading with a relatively preserved ability to read ideograms. The selective reading impairment of phonograms has been claimed to be characteristic in patients having alexia with agraphia due to a left angular gyrus lesion in some studies (Yamadori, 1975, 1979; Iwata, 1985; Yamadori *et al.*, 1985), among which only Yamadori's (1979) study had acceptable controls. According to our data, however, such a phonogram-ideogram dissociation is apparently rather unique and is far from being representative of the alexia with agraphia population. Most of the patients tested in the present study had unselective impairment of the two types of scripts. The reading disturbances of the cases with alexia with agraphia were relatively mild, which is consistent with our clinical impression that a relatively high performance level is characteristic of this population.

From the anatomical standpoint, the patient exhibiting a more severe disturbance of phonogram reading was not clearly distinguishable from the other patients. It appeared that the lesion in this case involved a slightly greater area of the occipital lobe than did the lesions in the other cases with unselective impairment of phonograms and ideograms. However, a similar occipito-temporal region was also destroyed in many of the pure alexics and Wernicke aphasics who displayed non-differential impairment of phonograms and ideograms. There appears thus to be no satisfactory neuroanatomical explanation for the distinct reading behaviour.

Recently, growing attention has been directed towards alexia with agraphia due to the damage occurring in the posterior part of the left middle or inferior temporal gyrus. It has been claimed that a disturbance of ideogram reading was caused by damage to the left middle temporal gyrus (Yamadori *et al.*, 1985; Mochizuki and Ohtomo, 1988) or the left posterior inferior temporal lobe (Iwata, 1984, 1985; Kawamura *et al.*, 1987; Kawahata *et al.*, 1988). A lesion in the posterior part of the left middle temporal gyrus (Yamadori *et al.*, 1985) or the left posterior inferior temporal lobe and the lateral occipital lobe (Kawahata *et al.*, 1988) has also been reported to have caused the alexia of phonograms. However, a closer examination of the past reports suggests that most of the studies cannot convincingly claim to show that a phonogram-ideogram dissociation existed. Some studies (Iwata, 1984, 1985; Yamadori *et al.*, 1985; Kawahata *et al.*, 1988) lacked descriptions of the stimulus materials or any qualitative data, while the data of Kawamura *et al.* (1987) failed to reach statistical significance at the 5% level when tested by the two-tailed Fisher's exact method. Furthermore, a large trial size (more than 400 trials), as in the study of Kawamura *et al.* (1987), produces a statistical significance or near-significance with just a small difference in performance level. Only the data of Mochizuki and Ohtomo (1988) appear sufficiently reliable.

We examined two cases with alexia with agraphia who had left temporal lobe lesions. The lesion site in one case (Case 6) was confined to the posterior parts of the left middle and inferior temporal gyri, and that in the other case (Case 7) extended from the left postero-inferior temporal region to possibly the white matter underlying the angular gyrus. In contrast to the patient of Mochizuki and Ohtomo (1988), who exhibited a more severe disturbance of ideogram reading, both of our cases showed that phonograms and ideograms were impaired to similar degrees. From the above discussions, the existence of a linkage between damage to the posterior part of the left inferior middle temporal gyri and a phonogram-ideogram dissociation must be in some doubt.

Numeral reading

The idea that reading numerals tends to be spared in pure alexics has been generally accepted since the days of Déjerine (1892). The present study showed that in no case were numerals read more erroneously than phonograms or ideograms. This tendency for numeral reading to be easier than non-numeral reading in some cases was also confirmed in testing with 10 phonograms, 10 ideograms and 10 numerals which were similar in their configurational complexity.

While numeral reading was found to be less impaired in several cases, a majority of our patients showed undifferentiated scores for numerals and non-numerals. The small sample size (10) in testing with single digits naturally lowered the probability of attaining statistical significance, and this may have obscured the ease of numeral reading relative to non-numeral reading. However, whether or not numeral reading is more spared may possibly vary from one patient to another. From the presence of the individual variations in phonogram and ideogram reading discussed so far, better reading of numerals is also likely to be subject dependent.

Neuroanatomical factors

Since various patterns of deficits in phonogram and ideogram reading were present even within one group, the possibility that symptomatology might be linked with any anatomical condition was examined. Specifically, the following three factors were considered: (i) the site of the lesion as identified by CT scans; (ii) whether the lesion was cortico-subcortical or subcortical; (iii) whether the aetiology involved cerebral haemorrhage or infarction. As mentioned previously, no overall relationships were recognized between any of these three variables and the individual performance traits concerning phonogram and ideogram reading within the population.

Two directions of dissociation, namely, a double dissociation between phonograms and ideograms found in the present study provided evidence that phonogram reading and ideogram reading are two separable processes. One of the dissociation types, the relative preservation of ideograms, may be interpreted as being supportive of the idea that phonological alexia is a distinctive process. Nevertheless, our results indicated that damage to nearly completely overlapping regions in the frontal lobe caused contradictory dissociation patterns. Employment of magnetic resonance imaging (MRI), rather than CT scans alone, may provide anatomical data which would demonstrate more convincingly the absence of an invariable correlation between lesions and a phonogram-ideogram dissociation pattern.

In an attempt to account for past findings concerning the phonogram-ideogram dissociation, Iwata (1984, 1985) assigned hypothetical routes for the reading of phonograms and ideograms to certain anatomical structures of the brain. It was proposed that the dorsal pathway via the angular gyrus is the route for phonogram reading, whereas the ventral pathway passing through the posterior part of the middle and inferior temporal gyri is the route for ideogram reading. In our data, one case with a lesion to the angular gyrus and/or its underlying white matter showed a greater disturbance of phonogram reading, which is consistent with Iwata's hypothesis. However, almost all of the cases with damage to the angular gyrus and its vicinity exhibited an unselective disturbance of phonogram and ideogram reading. Furthermore, the two cases with the middle and inferior temporal gyri also showed the absence of the phonogram-ideogram dissociation. Thus, our findings indicated that no such specific anatomical structures are strictly linked to the hypothetical phonogram and ideogram reading processes.

Another variable affecting reading performance was found to be the length of the period after the causal cerebrovascular accident. Performance patterns of the same patients often changed with the passage of time and, furthermore, the manner in which the post-onset time affected the reading performances was not consistent across patients. For example, one pure alexic patient (Case 2) initially at 40 d and 59 d post-onset showed no significant differences in reading performance for phonograms and for ideograms, but phonogram reading was found to be significantly better at 90 d post-onset. In contrast to the above pattern of recovery, however, one Wernicke aphasic patient (Case 2) initially exhibited a significantly more impaired reading of ideograms at 8 mths post-onset, but 2 mths later the phonogram-ideogram dissociation disappeared due to an impovement of ideogram reading. It is thus impossible to say whether a patient who exhibited a certain dyslexia pattern for phonograms and ideograms at one point in time will maintain the same impairment trait on other occasions or not. Individual variations seem to exist in the pathway of recovery as well as in the dyslexic syndrome. Taken together, our data indicate that no specific neuroanatomical conditions which are associated with lesions, performance levels or post-onset lengths are linked with a certain pattern of phonogram and ideogram disturbance in a straightforward manner. It should be added, however, that the possibility still cannot be totally excluded that specific reading disturbances might be explicable as interactions among the above variables. Further research is clearly needed so that additional data can be used to confirm or deny the possibility of such interactions.

So far, considerable emphasis has been placed on a link between lesion site and patterns of impairment. Not only have there been reports of alexia specific for either phonograms or ideograms, but there have also been reports of agraphia selective for Japanese phonograms or ideograms (Tanaka *et al.*, 1987; Kawamura *et al.*, 1989). Such studies on agraphia, however, are based on the performance of only a few cases, and the extent to which their patterns of impairment represent the whole population remains unknown. While sensory and motor dysfunctions can be neuroanatomically localized in affected individuals, impairments of certain high cortical functions, especially such complex ones as the reading of phonograms and ideograms, may not be correlated with damage to definite neuroanatomical structures. Due to the apparent individual variations, studies on reading behaviour must employ multiple subjects and take into account the possible individual variations. It is evident that we need to be cautious in drawing generalizations on the reading disturbance of phonograms and ideograms.

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THE INFLUENCE OF HANDEDNESS ON THE DISTRIBUTION OF MUSCULAR WEAKNESS OF THE ARM IN FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

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SUMMARY

The strength of 10 muscle groups in both arms was measured using hand-held myometry to determine the influence of handedness on left-right differences of muscle strength in facioscapulohumeral muscular dystrophy (FSHD). Two groups of subjects were studied: 24 healthy volunteers (19 right-handed), and 53 patients (42 right-handed) with autosomal dominant FSHD. An opposite left-right difference of strength of shoulder and arm muscles was found: right-handed volunteers were stronger on the right side, right-handed patients were stronger on the left side. This opposite left-right difference was statistically significant for the supraspinatus muscle, the wrist extensors and the shoulder internal rotators. The number of left-handed subjects was too small for statistical analysis. The relation between handedness and increased muscle weakness in right-handed FSHD patients suggests that mechanical factors may play a distinct role in the progression of muscle weakness in FSHD.

INTRODUCTION

Human myopathies, most often genetically determined, show a remarkable predominant proximal and symmetrical distribution of skeletal muscle weakness and wasting. One explanation for this distribution is their postural antigravity role: the proximal muscles are involved in eccentric contractions (i.e. lengthen during activity) to a much greater extent than are the distal muscles (Edwards *et al.*, 1984). Recent physiological studies have shown that eccentric contractions produce considerable muscle damage in normal healthy subjects (Newham *et al.*, 1983, 1986; Ebbeling and Clarkson, 1989). As a muscle becomes weaker and unable to meet the functional demands made upon it, the likelihood of accidental stretch becomes greater. This cycle of weakness, stretch, damage and further weakness may be the reason why the proximal muscles are the most severely affected in a wide range of myopathic disorders (Edwards *et al.*, 1984).

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominantly inherited disorder with a slowly progressive course and a descending order of muscle involvement (Padberg, 1982). Its severity can vary widely and asymptomatic cases are found in about 30% of the patients (Lunt, 1989). Facial weakness is often the earliest detectable sign,

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followed by muscle weakness in one or both shoulder girdles. Gradually, the foot extensors and muscles of the trunk and pelvic girdle become involved (Munsat, 1986). Associated symptoms include retinal vasculopathy (Fitzsimons *et al.*, 1987) and hearing loss (Voit *et al.*, 1986; Brouwer *et al.*, 1991). A distinct asymmetry of muscle involvement is frequently observed in FSHD (Carroll, 1979). This can be present in the facial muscles, in the shoulder muscles and in the extremities. It was repeatedly noticed that the right side was more affected than the left, and this triggered a discussion about a possible relationship between muscle weakness and handedness (Becker, 1953; Padberg, 1982). If this relationship really exists, it suggests that muscular weakness in FSHD might be increased by overuse or exercise.

The present study was undertaken to investigate whether asymmetry of muscle weakness of the shoulders and arms in FSHD patients could be documented using hand-held myometry, and whether this asymmetry was related to left- or right-handedness.

PATIENTS AND METHODS

The maximum voluntary contraction (MVC) of 10 muscle groups of both upper limbs was measured. Observations were made on healthy volunteers and on patients with autosomal dominant FSHD. The first group consisted of 24 subjects. None had a history of neurological abnormalities or recent muscle weakness or pain in the arms or shoulders. Fifty-three patients from nine families with well-defined autosomal dominant FSHD were studied as well. They had been studied earlier for linkage analysis and all showed linkage with the markers D4S171 and D4S139 which are located in the region $4q^{35}$-qter, indicating a homogeneous disorder in these families (Wijmenga *et al.*, 1990, 1991). Of each family at least one subject with clinical signs of FSHD had undergone extensive diagnostic procedures including electromyography and muscle biopsy, the results of which were all compatible with FSHD (Munsat, 1986). All patients were asked about the duration of recognized symptoms of facial or shoulder weakness. Children under the age of 15 yrs were excluded. Informed consent was obtained from all individuals enrolled in the study.

Muscle strength was measured with a hand-held myometer in the following muscle groups: flexors, extensors, abductors, external rotators and internal rotators of the shoulder; extensors and flexors of the elbow; extensors of the wrist; and flexors of the fingers and thumb using the three-point grip (van der Ploeg *et al.*, 1984) (Table 1). The abductors of the shoulder were measured in 10° abduction and in 90° abduction separately. The primary muscles of the 10 muscle groups studied are listed in Table 2. The dynamometer and the measurement technique have been described in detail elsewhere (Wiles and Karni, 1983; van der Ploeg *et al.*, 1984; Wiles *et al.*, 1990). In brief, the examiner places the dynamometer on the body part to be examined and applies gradually increasing counter force to overcome (and thereby lengthen slightly) the muscle group's action during the patient's best voluntary effort: the force recorded as the examiner overcomes the muscle contraction is taken as the peak force. The position of the body part and the dynamometer were standardized for each muscle group (Table 1). Each muscle group was tested three times with 10 s intervals between measurements. Maximum voluntary contraction was defined as the mean of three measurements (Whitley and Smith, 1963). The range of the dynamometer was 15–231 newtons. All measurements were carried out by the first author with the subject in supine position, with exception of the wrist extensors and three-point grip, which were examined in a sitting position. When a measurement of muscle strength was painful, the muscle group in question was excluded from the analysis.

To decide on left- or right-handedness, we used a standardized questionnaire for all subjects. They were asked to give their opinion about their handedness and to indicate which hand they used for writing; throwing a ball, dealing cards, brushing teeth and eating soup. For a definite conclusion about handedness, identical answers were necessary on at least the following three items: own opinion about handedness, and preferential hand for writing and brushing teeth (Plato *et al.*, 1984).

A multivariate analysis of variance (MANOVA) was used to compare the mean MVC scores for each muscle group of the subjects between left and right arms, and between patients and controls. Univariate and multivariate tests were used. The analysis was performed in SPSS-PC (V2.0) (Norušis, 1986) using a 'repeated measurements' approach; corresponding left and right measurements were treated as the 'within

TABLE 1 STANDARD POSITIONS FOR MUSCLE GROUPS TESTED

Muscle group	*Subject position*	*Position of part to be examined*	*Position of myometer*
Shoulder flexors	Supine	Shoulder flexed to 90°, elbow extended	Anterior surface of distal part of the upper arm
Shoulder extensors	Supine	Shoulder flexed to 90°, elbow extended	Posterior surface of distal part of the upper arm
Shoulder abductors (10°)	Supine	Arm abducted 10° and elbow extended	Lateral surface of distal upper arm
Shoulder abductors (90°)	Supine	Arm abducted 90° and elbow extended	Lateral surface of distal upper arm
Shoulder external rotators	Supine	Arm abducted at 90° and elbow flexed at 90°	Posterior surface of distal forearm
Shoulder internal rotators	Supine	Arm abducted at 90° and elbow flexed at 90°	Anterior surface of distal forearm
Elbow flexors	Supine	Arm alongside body, elbow flexed at 90°, forearm supinated	Anterior surface of distal forearm
Elbow extensors	Supine	Arm alongside body, elbow flexed at 90°, forearm supinated	Posterior aspect of distal forearm
Wrist extensors	Sitting upright	Forearm supported and pronated, wrist in neutral position, fingers flexed	Dorsal side of metacarpus, just proximal to third metacarpal head
Three-point grip	Sitting upright	Forearm pronated, wrist extended, distal half of thumb under applicator distal two-thirds of digits 2 and 3 above	Upright (not vertical or upside down)

subjects' effect. The group-comparison corresponds to the 'between subjects' effect. The interaction between these two effects was also studied. To ascertain the effect of left- or right-handedness on left-right differences of MVC, before this analysis the subjects were divided in a left- and right-handed group. Those subjects who were classified as uncertain with respect to left- or right-handedness were excluded from the study of left-right differences of MVC. Age and sex were included as covariates.

RESULTS

Subjects

Twenty-four healthy controls (16 males and eight females; mean age 36 yrs) and 53 patients with FSHD (35 males and 18 females; mean age 44.6 yrs) were studied. The mean duration of symptoms was 23 yrs (range, 0–54 yrs) in the male patients, and 19 yrs (range, 0–49 yrs) in the female patients; six males and two females were asymptomatic (Table 3). From the age of the patients and the duration of their symptoms the age at onset of first symptoms can be calculated, which in most cases lies between 15 yrs and 30 yrs. Many male patients had a working career that included heavy manual labour.

TABLE 2. PRIMARY MUSCLES OF THE 10 MUSCLE GROUPS STUDIED

Shoulder flexors (SF)	Deltoideus Pectoralis major Subscapularis
Shoulder extensors (SE)	Deltoideus Latissimus dorsi
Shoulder abductors (10°) (SAS)	Supraspinatus
Shoulder abductors (90°) (SAD)	Deltoideus
Shoulder external rotators (SER)	Infraspinatus Teres minor
Shoulder internal rotators (SIR)	Subscapularis Teres major
Elbow flexors (EF)	Brachialis Brachioradialis Biceps
Elbow extensors (EE)	Triceps
Wrist extensors (WE)	Extensor carpi radialis longus Extensor carpi radialis brevis Extensor carpi ulnaris
Three-point grip (TPG)	Abductor pollicis brevis Opponens pollicis Finger flexors

Handedness

From the 24 controls, 19 were right-handed (13 male, six female); 18 of them were right-handed on all items; one subject dealt cards with the left hand. One male was left-handed for all items; in four controls handedness was not definite. From the 53 patients, 42 were right-handed (26 male, 16 female); 39 of them were right-handed for all items; one was ambidextrous for throwing a ball; one was ambidextrous for eating soup; and one patient dealt cards with the left hand. Three patients fulfilled our criteria of left-handedness: one scored left-handed for all six items; one was ambidextrous for eating soup; and one was right-handed when throwing a ball and dealing cards. Five of the eight remaining patients regarded themselves as fully ambidextrous (Table 3).

Muscle strength

The strength of the 10 muscle groups was measured for both the right and left side in all subjects. Compared with controls, in patients certain muscle groups were notably weaker than others in males as well as in females (Fig. 1). The shoulder abductors (90°), shoulder anteflexors and to a lesser degree shoulder extensors were relatively more affected than other muscle groups, in both males and females. Other shoulder abductors (10°) were relatively spared in males, as were the wrist extensors and elbow extensors in females.

Left-right differences of muscle strength

The effect of handedness on the left-right difference between the muscle strength in both arms was analysed in right-handed subjects only, because the number of left-handers was too small for statistical analysis. The mean muscle strength of the 10 muscle groups in right-handed patients and controls is listed in Tables 4 (males) and 5 (females).

In right-handed patients, the mean muscle strength was greater on the left side, with the only exception being elbow flexors in males and the shoulder external rotators in females. In right-handed controls, the mean muscle strength was greater on the right, with the exception of the shoulder extensors in females. The question as to whether

TABLE 3. CLINICAL CHARACTERISTICS AND MUSCLE STRENGTH OF FSHD PATIENTS

Patient no	Sex (M/F)	Age (yrs)	Duration of symptoms (yrs)	Handedness (R/L)	Manual work	*Maximum voluntary contraction (newtons)*									
						SF		*SE*		*SAS*		*SAD*		*SER*	
						R	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*
1	M	17	0	R	–	231	231	231	231	231	231	231	231	188	119
2	M	23	0	R	+	231	231	231	231	231	231	231	231	231	231
3	M	31	0	R	+	182	136	231	231	231	231	181	126	209	205
4	M	33	0	R	–	156	231	162	231	204	231	231	231	116	231
5	M	33	0	R	–	178	166	188	188	231	188	188	166	188	209
6	M	21	1	R	+	231	231	231	231	231	231	231	231	199	231
7	M	46	6	R	+	85	91	139	231	231	Pain	88	Pain	136	Pain
8	M	26	9	R	–	187	231	231	231	231	209	152	144	209	231
9	M	26	9	R	–	201	169	231	231	231	231	121	133	231	166
10	M	39	20	R	–	36	36	98	114	179	231	56	65	108	110
11	M	42	22	R	+	106	80	144	159	231	231	113	91	144	168
12	M	42	25	R	+	45	36	72	101	145	150	72	61	130	108
13	M	44	26	R	+	15	36	39	72	231	231	71	56	101	81
14	M	48	27	R	–	15	15	36	42	88	124	15	15	65	51
15	M	44	28	R	–	15	Pain	51	Pain	144	82	48	Pain	94	Pain
16	M	53	30	R	+	Pain	Pain	Pain	Pain	Pain	Pain	Pain	Pain	Pain	Pain
17	M	52	35	R	–	15	15	15	41	155	137	36	41	77	54
18	M	67	37	R	+	41	107	143	166	189	177	52	77	68	64
19	M	55	40	R	–	15	15	59	36	94	143	15	15	15	46
20	M	60	40	R	+	Pain	Pain	15	15	185	100	80	90	84	74
21	M	64	44	R	–	15	117	59	68	166	188	72	116	72	137
22	M	68	49	R	+	39	163	68	93	179	201	15	124	88	162
23	M	70	50	R	–	15	15	56	49	91	153	15	15	42	39
24	M	70	54	R	+	15	15	29	102	95	145	15	15	36	44
25	M	31	?	R	–	15	15	15	15	94	155	15	52	36	32
26	M	39	?	R	+	155	87	166	231	231	144	78	54	126	117
27	F	15	0	R	–	126	196	182	163	107	129	78	82	146	106
28	F	33	0	R	–	134	144	120	119	88	130	94	77	124	121
29	F	30	6	R	+	84	75	127	136	120	108	71	56	80	65
30	F	62	6	R	–	97	81	48	155	100	117	94	91	90	114
31	F	69	9	R	–	74	101	101	144	108	113	67	64	107	91
32	F	23	13	R	–	49	98	144	157	125	189	55	68	95	51
33	F	37	16	R	–	84	61	129	152	140	163	90	71	133	111
34	F	30	19	R	–	36	59	121	82	121	135	36	52	56	68
35	F	39	23	R	–	15	15	41	58	118	131	52	48	64	59
36	F	43	24	R	+	55	15	82	98	71	121	62	42	65	59
37	F	44	24	R	–	53	181	140	168	130	130	39	149	72	140
38	F	62	32	R	–	64	101	152	166	114	122	69	82	85	108
39	F	54	39	R	–	15	15	36	41	58	46	15	15	15	36
40	F	59	39	R	–	15	15	15	15	15	15	15	15	15	15
41	F	55	49	R	–	100	62	107	129	123	116	56	82	54	61
42	F	70	?	R	–	153	157	153	136	129	121	74	103	156	134
43	M	28	0	L	+	186	231	188	231	188	188	111	121	209	231
44	M	43	22	L	–	106	51	134	165	188	231	82	71	136	136
45	M	42	32	L	–	15	15	15	15	15	15	15	15	15	15
46	M	31	9	R+L	+	111	103	15	15	231	101	102	93	72	82
47	M	31	15	R+L	–	41	71	84	163	209	209	71	106	209	143
48	M	39	23	R/L	–	15	15	133	153	137	231	147	110	136	136
49	M	42	24	R/L	–	15	15	62	51	103	88	71	78	72	74
50	M	55	32	R+L	+	15	15	88	93	231	231	88	82	52	84
51	M	64	49	R+L	+	36	15	45	69	97	160	41	58	61	88
52	F	45	9	R/L	–	15	Pain	23	Pain	15	Pain	Pain	Pain	45	Pain
53	F	75	15	R+L	–	Pain	Pain	65	Pain	97	Pain	Pain	Pain	Pain	Pain

TABLE 3 (*continued*)

Patient no	*Sex (M/F)*	*Age (yrs)*	*Duration of symptoms (yrs)*	*Handedness (R/L)*	*Manual work*	*Maximum voluntary contraction (newtons)*									
						SIR		*EF*		*EE*		*WE*		*TPG*	
						R	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*
1	M	17	0	R	–	231	149	231	217	172	153	166	117	121	116
2	M	23	0	R	+	231	231	231	231	231	231	231	231	231	231
3	M	31	0	R	+	231	231	231	231	199	127	231	231	134	142
4	M	33	0	R	–	88	231	100	191	95	155	108	231	95	168
5	M	33	0	R	–	188	209	231	231	137	166	166	188	82	85
6	M	21	1	R	+	231	231	231	231	231	224	231	169	113	106
7	M	46	6	R	+	153	Pain	231	231	121	127	163	133	56	88
8	M	26	9	R	–	231	231	231	231	188	188	188	188	117	103
9	M	26	9	R	–	231	231	231	231	231	231	139	130	144	116
10	M	39	20	R	–	126	166	231	231	130	170	100	231	74	121
11	M	42	22	R	+	231	195	231	231	94	134	72	179	80	133
12	M	42	25	R	+	88	131	159	191	90	114	198	130	103	130
13	M	44	26	R	+	121	144	165	69	15	15	113	147	87	90
14	M	48	27	R	–	62	101	15	15	15	15	15	15	62	65
15	M	44	28	R	–	65	Pain	15	15	15	15	61	52	54	56
16	M	53	30	R	+	Pain	Pain	166	166	Pain	Pain	Pain	Pain	51	75
17	M	52	35	R	–	116	98	206	231	15	15	15	113	56	90
18	M	67	37	R	+	126	91	189	186	107	111	179	185	100	82
19	M	55	40	R	–	49	114	87	15	41	15	15	46	69	51
20	M	60	40	R	+	48	64	Pain	Pain	Pain	Pain	Pain	Pain	46	15
21	M	64	44	R	–	38	72	172	134	56	41	61	155	22	67
22	M	68	49	R	+	98	107	136	185	127	98	124	163	75	64
23	M	70	50	R	–	81	64	15	15	15	15	15	46	15	15
24	M	70	54	R	+	46	68	140	121	62	64	71	81	59	68
25	M	31	?	R	–	22	52	15	15	15	15	15	15	32	29
26	M	39	?	R	+	176	169	231	198	137	176	231	188	111	100
27	F	15	0	R	–	114	97	146	163	123	143	62	78	75	90
28	F	33	0	R	–	136	116	182	192	123	107	149	140	78	81
29	F	30	6	R	+	93	124	162	46	108	107	130	111	106	78
30	F	62	6	R	–	80	95	130	162	85	137	111	120	41	49
31	F	69	9	R	–	87	116	120	108	104	101	95	93	71	71
32	F	23	13	R	–	98	107	143	176	71	91	113	Pain	93	87
33	F	37	16	R	–	100	107	186	194	104	146	129	166	58	54
34	F	30	19	R	–	88	15	124	168	134	72	93	140	56	87
35	F	39	23	R	–	100	95	15	15	101	91	64	94	45	62
36	F	43	24	R	+	84	100	97	131	97	85	78	101	78	62
37	F	44	24	R	–	137	169	153	183	137	231	163	172	64	69
38	F	62	32	R	–	108	106	183	166	156	176	159	159	69	84
39	F	54	39	R	–	36	82	15	15	15	15	15	15	35	44
40	F	39	39	R	–	15	15	15	15	15	15	15	15	15	15
41	F	55	49	R	–	101	97	140	106	91	75	126	120	29	15
42	F	70	?	R	–	131	108	183	170	136	116	129	186	90	94
43	M	28	0	L	+	188	209	231	231	188	188	231	231	129	131
44	M	43	22	L	–	149	231	231	231	163	160	117	62	140	77
45	M	42	32	L	–	61	100	15	15	15	15	42	36	15	15
46	M	31	9	R+L	+	45	91	15	32	15	15	15	68	62	46
47	M	31	15	R+L	–	123	231	231	231	201	209	104	209	71	88
48	M	39	23	R/L	–	108	150	45	104	36	108	97	146	87	101
49	M	42	24	R/L	–	58	139	15	15	15	15	59	45	68	61
50	M	55	32	R+L	+	90	123	15	45	15	49	15	142	69	82
51	M	64	49	R+L	+	74	69	15	15	15	15	36	41	15	15
52	F	45	9	R/L	–	80	Pain	58	Pain	61	Pain	54	Pain	15	Pain
53	F	75	15	R+L	–	Pain	Pain	108	Pain	68	Pain	62	Pain	56	15

Handedness R is right-handed, L is left-handed, R+L means that subjects regard themselves as fully ambidextrous, R/L means handedness not definite Manual work – is light or administrative manual work, + is heavy manual work Maximum voluntary contraction is the mean of three separate measurements, 'pain' means that the measurement was painful, and was excluded from the analysis For abbreviations of the muscle groups *see* Table 2

the difference between left and right arm is the same in patients and controls was solved by applying a statistical test for interaction between these two effects. This interaction appeared to be highly significant and indicated opposite effects in patients and controls (Table 6). For shoulder abductors (10°) and wrist extensors, the difference was very

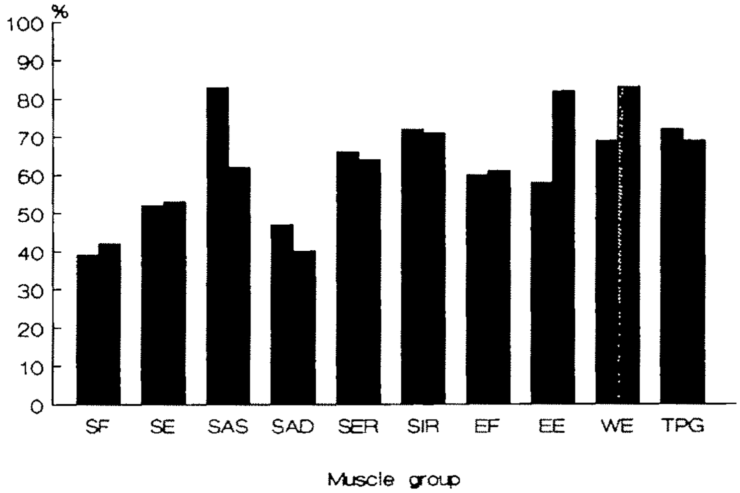

FIG. 1. Mean MVC of 10 shoulder girdle and arm muscle groups in FSHD patients (male, n = 35, black columns; female, n = 18, hatched columns) expressed as a percentage of the mean MVC in control subjects. Values for the right and left side have been combined. For abbreviations of muscle groups *see* Table 2

TABLE 4 MUSCLE STRENGTH IN RIGHT-HANDED MALES

	FSHD patients (n = 26)		*Controls (n = 13)*	
	Right	*Left*	*Right*	*Left*
Shoulder flexors	93±85	107±84	233±27	227±40
Shoulder extensors	118±82	139±84	239±27	230±30
Shoulder abductors (10°)	182±54	182±47	218±32	215±33
Shoulder abductors (90°)	97±77	103±74	207±48	201±43
Shoulder external rotators	120±65	126±71	184±35	177±41
Shoulder internal rotators	132±75	147±66	205±37	194±36
Elbow flexors	165±80	162±85	244±17	235±23
Elbow extensors	106±75	109±77	180±32	172±29
Wrist extensors	121±77	140±68	190±37	175±37
Three-point grip	84±45	92±47	119±25	113±27

Maximum voluntary contraction (newtons) of 10 muscle groups (mean ± SD), left and right arm separately

significant ($P = 0.003$ and $P = 0.009$, respectively), and for shoulder internal rotators significant ($P = 0.012$). For shoulder flexors and shoulder external rotators, the difference was not significant ($P = 0.335$ and $P = 0.301$, respectively).

In the three left-handed patients no left-right preference of muscle strength was found. The eight patients with no definite handedness showed the same trend as the right-handed patients, the muscles at the left side being stronger than those on the right (Table 3).

TABLE 5 MUSCLE STRENGTH IN RIGHT-HANDED FEMALES

	FSHD patients (n = 16)		*Controls (n = 6)*	
	Right	*Left*	*Right*	*Left*
Shoulder flexors	72±43	86±59	187±26	178±16
Shoulder extensors	106±49	120±48	206±25	214±21
Shoulder abductors (10°)	104±32	118±40	195±42	151±25
Shoulder abductors (90°)	60±25	69±33	175±40	160±36
Shoulder external rotators	85±42	84±37	134±33	127±22
Shoulder internal rotators	94±32	97±37	140±20	130±23
Elbow flexors	125±60	126±67	210±32	195±27
Elbow extensors	100±40	107±54	126±16	116±23
Wrist extensors	102±46	114±51	131±21	117±13
Three-point grip	63±25	65±25	92±18	89±19

Maximum voluntary contraction (newtons) of 10 muscle groups (mean ± SD), left and right arm separately.

TABLE 6 MUSCLE GROUPS FOR WHICH PATIENTS AND CONTROLS ARE SIGNIFICANTLY DISSIMILAR IN THEIR 'LEFT-RIGHT DIFFERENCE IN MUSCLE STRENGTH'[1]

Muscle group	*P*
Shoulder extensors	*
Shoulder abductors (supraspinatus)	**
Shoulder internal rotators	**
Elbow extensors	*
Wrist extensors	**

*$P < 0.10$; **$P < 0.05$, univariate tests averaged over females and males; multivariate (overall) $P = 0.03$. [1]The magnitude of the effect can be seen in Tables 3–5 for females and males separately.

DISCUSSION

The most widely accepted method of describing muscle strength is that using the MRC (Medical Research Council) scale. However, the MRC scale with its semi-quantitative nature is subject to several limitations, not least the fact that the grades are not equally spaced, grades 3–5 covering a very broad range of muscle force and hence of functional capacity (Edwards and Hyde, 1977; van der Ploeg *et al.*, 1984). Hand-held myometry, on the other hand, can express strength in a quantitative manner and normal values for male and female healthy adults have been obtained (van der Ploeg *et al.*, 1991). It is applicable in nearly every clinical setting, is rather similar to manual strength testing and is available at low cost. In healthy volunteers, aged 20–60 yrs, there was no significant influence of age, weight or height on the muscle strength of most muscle groups (van der Ploeg *et al.*, 1991).

We measured the strength of shoulder girdle and arm muscles in a large group of FSHD patients using hand-held myometry. The method of measuring muscle strength of the shoulder girdle muscles in a supine position proved to be very useful because many FSHD patients are not able to lift their arms up to 90° in a sitting or standing position. In addition to being of greatest comfort for the patients, this position reduces the influence of scapular winging and gravity, and it allows better standardization of the measurements. However, it is not known precisely which muscles are effective in FSHD patients when the different muscle groups are tested. A conclusion about muscle strength based on these measurements can therefore only be given on muscle groups, and not on specific primary muscles.

In both male and female FSHD patients, we found that the abductors (90°), flexors and extensors of the shoulders were affected most (Fig. 1). Insufficient scapular fixation could play a role, because even with the patients in supine position, glenohumeral movement could not be assessed independently from scapulothoracic movement. Other shoulder abductors (10°) were relatively spared in males. This finding contradicts earlier reports of frequent involvement of the supraspinatus muscle (Bradley, 1979). The external rotators of the shoulder were relatively more affected than the internal rotators which might at least partially explain the commonly occurring internal rotation of the arms in FSHD patients. Sparing of the forearm muscles was found in both males and females. In females the wrist extensors and elbow extensors especially were relatively strong. The shorter duration of symptoms (mean 19 yrs) in females compared with that in males (mean 23 yrs) may explain this finding to some extent, as these muscles are mostly affected later during the course of FSHD.

In controls, the mean female/male ratio of muscle strength of the different muscle groups was about two-thirds. This compares well with the findings of other authors in healthy subjects (van der Ploeg *et al.*, 1991). The same ratio was found in the FSHD patients, which suggests that there is no sex preference of muscle weakness in FSHD.

A striking feature of FSHD is the asymmetry of muscle involvement. A left-right variation of muscle strength is quite normal, but in healthy volunteers it usually does not exceed 20% in either direction (van der Ploeg, 1991). Becker (1953) noted that in FSHD patients the right side was more involved than the left one in 30% of his cases, the left side more than the right one in 15%, while in 55% of his cases both sides were more or less equally affected. His criteria for asymmetry were an asymmetric configuration of the shoulder, an asymmetric strength on arm abduction, and an asymmetric onset of muscle weakness. He considered this asymmetry to be a strong argument for environmental influences on the expression of the gene, but he did not mention the possibility of a relation with right or left handedness. Padberg (1982) considered asymmetry to be present if the strength of similar muscles on the right and left side differed 1 degree or more on the MRC scale, if either side was graded 4+ and the other 4− on the MRC scale or if there was a distinct difference in muscle atrophy. He found a preference for right-sided shoulder girdle or arm weakness in 39 of 107 patients. After correction for the asymmetry of the handedness distribution in the population, this proved not to be statistically significant ($P = 0.055$).

Manual preference can be assessed relatively easily either by questionnaire or by tests of performance (Geschwind and Galaburda, 1985). An accurate determination of handedness may even be made by simply testing for handwriting or by asking participants if they are left- or right-handed (Plato *et al.*, 1984). We used a combination of identical answers on at least three items (*see* Methods) on a questionnaire to indicate left- or right-handedness in our subjects. The answers on the different items for handedness correlated strikingly well: 39 (93%) of the 42 patients, and 18 (95%) of the 19 controls, all of them having been identified as right-handers, scored right-handed on all items including those dealing with proximal throwing movements.

A distinct relationship between left-right differences of shoulder girdle and arm muscle strength, and handedness was found. Although the mean left-right differences were relatively small in both controls and patients, they pointed in the same direction in almost all muscle groups: right-handed controls were more often stronger on the right side, right-handed FSHD patients were more frequently stronger on the left side. This was found in males as well as in females. This effect was statistically significant for shoulder abductors (10°), shoulder internal rotators and wrist extensors ($P < 0.05$). However, some right-handed FSHD patients were stronger on the right side for certain muscle groups. The same was true for right-handed control cases, some of them going against the general trend of being stronger on the right side.

There is a clear relationship between age, duration of recognized symptoms, and the severity of muscle weakness. The first symptoms of facial and/or shoulder weakness are generally noticed between the age of 15 yrs and 30 yrs. The measurements of muscle strength in the patients showed a gradual decrease with longer duration of symptoms. No correlation was found between age, duration of symptoms or the degree of upper limb weakness on the most severely affected side and the degree of asymmetry in muscle strength. The asymptomatic patients showed the same trend of asymmetry as the patients with clinical symptoms of FSHD. Of the male patients, surprisingly many did or had done heavy manual work. Most of them had to stop this kind of work before the age of 35 yrs.

One of our patients, a right-handed carpenter, complained of progressive weakness of his right shoulder and arm muscles which, in his own opinion, was due to the heavy use of his right arm. This patient focused our attention to an intriguing problem, and in the following years we saw many patients with similar complaints. When the relationship between muscle weakness and handedness is used as a model for testing the effect of exercise or even overload on muscle strength, our findings suggest that in FSHD patients more use of muscle groups may lead to greater weakness of these muscles. This finding corresponds to our personal experiences with FSHD patients. On the other hand, we have no knowledge of FSHD patients who had an increase of muscle strength during the course of an exercise programme.

It is not clear why the negative effect of exercise is more distinct in certain muscle groups, but those muscle groups remaining relatively stronger in the patients, seem to be most frequently involved. This may be due to the fact that the stronger muscles are more exposed to exercise-induced damage. Another theoretical possibility is that a primary weakness in one shoulder girdle muscle results in a secondary overuse and weakness in another.

Related to the problem under study, an important and difficult question often asked by patients with muscular dystrophy, is whether they should exercise their still strong or already weak muscles. There has been considerable concern for many years that exercise, especially strengthening exercise, accelerates weakness in some motor unit diseases (Fowler and Taylor, 1982). Most human studies have dealt with Duchenne muscular dystrophy, and the results reported are difficult to interpret since (i) subjective measurements were usually used, (ii) there were rarely any controls, and (iii) normal growth patterns or the natural course of the disease were usually ignored. Some reports suggested modest gains with strengthening exercises (e.g. Vignos and Watkins, 1966), while others found little or no improvement (Scott *et al.*, 1981). Two major factors appear to be critical in weakness due to overwork or heavy exercise: the first is the effect of the degree of weakness at the time the exercise programme was started; the second is the type and, especially, the intensity of the exercise training programme (Fowler and Taylor, 1982).

The findings of this study suggest that the typical profile of shoulder girdle and arm muscle weakness in FSHD represents the genetic predisposition of specific muscles to become more or less affected. Our finding of a relationship between asymmetry of shoulder and arm muscle weakness and handedness suggests that mechanical factors may also play a role in the development and progression of muscle weakness in FSHD. Therefore, in our opinion, training programmes in FSHD patients should be monitored carefully.

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BOOK REVIEWS

Cajal's Degeneration and Regeneration of the Nervous System. Edited by Javier DeFelipe and Edward G. Jones. 1991. Pp. 769. New York: Oxford University Press. Price £60.00.

The Oxford University Press has chosen as the fifth of its series of books on the History of Neurosciences, a new edition of Raoul May's English translation of Ramon Y. Cajal's *Degeneration and Regeneration of the Nervous System.*

Ramon Y. Cajal must be regarded as the greatest neurohistologist and it is welcome news that this classic work has been reissued. The book has been unavailable for some years, so that many of today's neuroscientists will never have had the opportunity to read this remarkable work.

Cajal's studies on the degeneration and regeneration of the nervous system were made at the mid-point of his long and productive scientific life. It was at about the time of these studies (1906) that he was awarded (jointly with Professor Camillo Golgi) the Nobel Prize for the section of Medicine and Physiology; the Prize had never before been given to histologists.

In his autobiography (*Recollections of My Life*) Cajal recorded receiving the news of his award with 'fear and displeasure'. He knew that such an honour would severely disrupt his life, and said that he was tempted to refuse it. However, accept it he did, together with the many unwanted attentions it bought, including, even then, having 'chocolates, cordials and potions of doubtful hygiene' named after him. But there were many agreeable tributes and among them was the offer, from medical compatriots in the Argentine Republic, to pay for the publication of a book on his work. Cajal soon realized that a great deal of reorganization would be required to adapt a compilation of published facts into a book which would be worthy of the generosity of his fellow-countrymen. The first volume of the book was finally published in 1913 and the second volume in 1914. The book described most of his investigations into the degeneration and regeneration of the nervous system, which, of his many and varied studies, he considered to be some of the most important and detailed.

A limited number of copies of the book were published, most of which Cajal seems to have given away, and a further printing did not materialize due to the outbreak of World War I. In 1928, Oxford University Press published an English version translated 'out of enthusiasm' by Raoul Michel May, a biologist who had himself worked on nerve regeneration under the direction of Detwiler in the USA. Facsimile reprints were published in the USA in 1959 and 1968.

The editors of this new edition, Javier DeFelipe and Edward G. Jones, have set the scene for the book with a few introductory chapters of particular relevance. These include parts of two chapters from Cajal's autobiography *Recollections of My Life*, which did not appear in the English translation by E. Horne Craigie, but which relate to the periods during which Cajal was working on nerve degeneration and regeneration. One translated paper describes the photography of nerve fibre degeneration, and another shows how the findings of nerve regeneration support the 'neuron' theory, the concept which dominated Cajal's work. Then there is the text of a series of memorial lectures to Cajal given in 1935 by Tello, one of Cajal's most brilliant students who made his own important contributions in the field of nerve regeneration.

The editors of the present version have identified and listed some errors in the translation but generally it was found to be very accurate. A corrected bibliography in modern format completes Part 1, the introductory section. Part 2 is a facsimile of both volumes of the Oxford University Press version of 1928.

Ramon Y. Cajal was born in 1852 in a small village in Navarre in north-east Spain. His father, who eventually qualified as a surgeon, showed the characteristics of perseverance, ambition and an acute sense of observation which also became highly developed in his son. Cajal's father did not encourage the undoubted artistic talents of his son, which were to prove of such value in later life, but he willingly offered his help once Cajal had begun his medical studies in Zaragoza.

Cajal was inspired by the microscopical preparations he was shown when taking his examinations in Madrid. He bought a microscope and microtome and began working on his own, but with guidance from Ranvier's book *Tratado de Tecnica Histologica*. He became interested in bacteriology because of the cholera epidemic of 1885, and his experiments culminated in the first published demonstration of the effects of the inoculation of dead cultures of the causative bacillus. But, for economic reasons, Cajal finally chose to study histology—the materials were less expensive.

Cajal obtained the Chair of Histology in Barcelona and here he learnt the method, described by Golgi, the famous histologist from Pavia, in which, for some curious reason still not understood, certain nerve cells are stained in their entirety, down to the finest of the nerve terminations, whilst other nerve cells are left completely unstained. Cajal applied this method, initially to tissues from the cerebellum, and showed that the terminal parts of axons all end in free arborizations, such as baskets or climbing branches, which are very closely apposed to the cell bodies and dendrites of contacting nerve cells. His particular success lay in the use of immature animals whose developing nervous system was more simple to study than the hopelessly complex organization of the mature animal.

At this time a fierce controversy raged between two opposing views of nervous system organization. (The vehemence of this controversy comes through in Cajal's writing.) The 'neuron' theory, advanced firstly by Waldeyer, and then by His and Forel, held that each neuron was a structural and functional unit. The alternative 'reticular' theory, supported by most neurohistologists of the time, saw the arrangement of nerve elements as a continuous network. Cajal's studies using the Golgi method provided at that time the most compelling evidence in favour of the 'neuron' theory. (Conclusive evidence of the theory was not available until the demonstration by electron microscopy of the synaptic cleft separating two neurons.)

However, confident of his overthrow of the 'reticular' theory, Cajal was appalled when arguments over theories of nerve regeneration, which implicated the 'neuron' theory, re-emerged as a result of his studies on peripheral nerve regeneration.

Cajal's book opens with an overview of the opposing theories of nerve regeneration. Controversy had continued for over 30 yrs between monogenists and polygenists; the former held that in regeneration, axons from the proximal stump of a severed nerve, still in continuity with their cell bodies, produce sprouts which grown into the peripheral stump forming the regenerated nerves. This was in agreement with the proponents of the 'neuron' theory who had suggested that in development nerve fibres are formed as outgrowths from the parent neuron. The opposing, polygenist view held that, in regeneration, nerve fibres arose autonomously from chains of Schwann cells in the peripheral stump, later fusing with those of the central stump. Developmental hypotheses in opposition to the 'neuron' theory, had proposed that newly growing fibres are formed by a similar process.

Cajal's success in promoting the monogenist view lay in the histological methods he used to study the problem. He perfected reduced silver methods for the impregnation of axons. Techniques used by other neurohistologists did not show the fine axons so beautifully demonstrated with Cajal's reduced silver methods. As a result, regeneration in peripheral stumps, which in some cases had been identified electrophysiologically, had seemed to occur in the absence of any morphological nerve connection between the divided central and peripheral ends of the nerve. Cajal showed that even when the central and peripheral ends were widely separated, fine axons, without accompanying Schwann cells, could be demonstrated crossing the divide.

A full description of the reduced silver methods for impregnation of axons, and other techniques commonly employed by Cajal form the second chapter of the book. The following chapter gives an account of the structure of the normal myelinated fibre, and is largely based on the work of others, particularly Ranvier and Nageotte. With the advantages of a multitude of new techniques, we can now, with hindsight, appreciate thè remarkable accuracy of these descriptions. However, description is one thing, and interpretation another. Cajal did not regard myelin as being in any way related to the Schwann cell; he described myelin as 'an adjunct of the axon . . . entirely foreign to Schwann's cell'. He arrived at this conclusion from the fact that myelin was formed in the central nervous system in the absence of Schwann cells. It might also be suspected that to suggest involvement of the Schwann cell in the formation of a structure so integral to the nerve fibre smacked too much of a 'polygenist' mechanism. It seems possible that Cajal had never come across the work of Gombault who in 1880/1881 showed demyelination and remyelination in peripheral nerves in lead-poisoned guinea-pigs. It would be difficult to escape the conclusion from this work, also beautifully illustrated, that the Schwann cell is associated with the myelin sheath.

The remainder of this first volume is devoted to the detailed description of experimental studies in fibre degeneration and regeneration. Cajal's style of writing seems verbose by modern standards, yet he conveys to the page, the pictures he sees, with an unsurpassed vitality and clarity. Throughout the book, Cajal refers to, acknowledges, and criticizes, the work of others who have contributed to this field of research. However, he is always at pains to stress those instances in which his own findings antedate those of his 'rivals'.

The morphological changes in Wallerian degeneration, in unmyelinated, as well as myelinated fibres are described in remarkable detail. But it is the studies of axonal regeneration which were, and remain, of greatest importance. Apart from their relevance to the monogenist argument, they led Cajal to the conclusion that the proliferated Schwann cells in the distal stump could produce a neurotrophic substance, a hypothesis confirmed in recent years by the demonstration of nerve growth factor in these cells. Cajal recognized that this was a 'non-specific' trophic factor. He suggested possible rearrangement of central connections following incorrect peripheral regeneration, although he felt that the non-regenerability of the central nervous system would not allow this.

Cajal was aware of the importance of the continuity of the Schwann cell-filled tubes or Bands of Büngner in regeneration following injury which did not sever the nerve.

The different forms and routes of regenerating sprouts are wonderfully displayed in Cajal's preparations. An almost identical picture of sprouting fibres proximal to nerve section was obtained relatively recently by reconstruction of semi-serial electron micrographs of five fibres, an exercise which took almost 2 yrs to complete.

Cajal's studies on regeneration, too numerous to mention, included the effects of ligatures of varying tightness, of combinations of ligatures and nerve section, complete and incomplete, of proximal-proximal anastomoses and many nerve grafting experiments. These were all interpreted as confirming the 'monogenist theory and/or providing evidence of a principle of neurotropism.

Cajal was more interested in the demonstration of axons than of the myelination of regenerated fibres, which according to his descriptions often seems very delayed and incomplete. Thin myelin sheaths would not have been readily identifiable in his silver preparations.

Cajal's illustrations are superb, although, probably through carelessness, he occasionally reverses the polarity of his drawings so that whilst the majority have the proximal end of a nerve fibre at the top, it is occasionally the reverse.

The second volume has the subheading 'Degeneration and Regeneration of the Nerve Centres'. This includes firstly a section on dorsal root and sympathetic ganglia; which he obviously considered to be part of the central, rather than peripheral nervous system. The normal appearances of the ganglion cells are described; Cajal records that he was one of the first to recognize satellite cells, although their role in replacing degenerate ganglion cells was already known to Nageotte. Cajal attempted subcutaneous grafting of dorsal root ganglia, with more success than others because of his use of small ganglia from young animals. The cells produced axons but did not survive for long.

One of the main objects of Cajal's central nervous system research was to discover whether regeneration was possible. He made lesions in the dorsal columns of the cord, the optic nerve and the cerebral and cerebellar cortex. His findings are again too numerous to mention. Of importance was the evidence of growth of new naked axons; although these often did not survive, and the demonstration of survival of terminal nests of basket cells, despite degeneration of the associated Purkinje cells; both findings providing further ammunition against the reticularists. Cajal discovered that a nerve cell will survive trauma to its processes provided that this occurs beyond the emergence of recurrent collaterals. His work on cord lesions near to nerve roots, showing regeneration of central axons into the roots, confirmed his belief that the Schwann cells produce a neurotrophic factor and that no similar factor was to be found in the central nervous system.

Mention must be made of the grafting experiments involving insertion of a peripheral nerve into the optic nerve or to other sites of central nervous system lesions. These had been undertaken by many other workers, and Tello was much involved in the studies reported here by Cajal. The evidence of growth of central axons into the peripheral graft provided further confirmation of the neurotrophic effects of a component of peripheral nerve, probably the proliferating Schwann cells.

These experiments also showed that central nervous system axons have the potential to regenerate, given the appropriate conditions. Cajal realized that central nervous system regeneration was, for all practical purposes at that time, an impossibility, but he predicted that 'It is for the scientist of the future to change . . . this harsh degree'.

We must be grateful to Javier DeFelipe and Edward Jones, who having already edited a reissue of Cajal's great work on the cerebral cortex, the first in this History of Neurosciences series, have now made available Cajal's other *magnum opus* to the ever-increasing numbers of neuroscientists for whom it should be essential reading. The 'neuron' and 'monogenist' theories no longer evoke the passionate response that they did in Cajal's time, but confirming them provoked an enormous amount of research much of which is still highly relevant.

JEAN M. JACOBS

Neglect and the Peripheral Dyslexias. Edited by M. J. Riddoch. 1991. Pp. 338. New Jersey: Lawrence Erlbaum Associates. Price $69.95

This book combines two issues of the Journal *Cognitive Neuropsychology* (1990 and 1991), edited by Jane Riddoch, devoted to 'neglect and the peripheral dyslexias'. It opens with an introduction by Riddoch, who lists the recurring themes, and summarizes the main empirical findings, theoretical positions and areas of controversy. It is concerned with two types of reading impairment produced by brain damage acquired in adult life: neglect dyslexia and letter-by-letter reading (pure alexia).

A first lesson to be learned from the book is that the clinical labels 'neglect' and 'letter-by-letter' dyslexias are not likely to refer to single deficits but include instead a number of different types of impairment. Consider first neglect dyslexia, where the reported evidence supporting a fractionation of the disorder is perhaps more compelling. Caramazza and Hillis report data from a left-handed left brain-damaged patient with a reading impairment concerning the right part of words, independent of topographic transformations of the physical stimulus (vertical, mirror-reversed). They conclude that a canonical, word-centred spatially defined graphemic representation is affected. By contrast, the left reading deficit of the right brain-damaged patient of Young, Newcombe and Ellis vanishes when the words are presented in vertical orientation, suggesting an impairment involving the representation of left space. Neglect dyslexia, in addition, is not the mere manifestation in the domain of reading of a more pervasive disorder concerning the space contralateral to the lesion. The patients of Caramazza and Hillis and of Young *et al.* show neglect also in non-reading tasks, such as line bisection or item cancellation. The left brain-damaged patient of Warrington, by contrast, displays right neglect in reading, but not in cancellation and drawing tasks. The puzzling left brain-damaged patient investigated by Patterson and Wilson frequently fails to identify the initial (left) letter of words, but does not show visuo-spatial neglect.

Case studies of letter-by-letter reading are reported by Kay and Hanley, Rapp and Caramazza, Farah and Wallace. Kay and Hanley explain the impairment of their patient in terms of an inability to identify more than one letter at the same time. In a left brain-damaged patient, Rapp and Caramazza show a difficulty in detecting right-sided letter and non-letter stimuli, explained in terms of deficits at the retino-centric and stimulus-centred levels of representation, and attempt to relate the patient's letter-by-letter disorder to this kind of impairment. Farah and Wallace suggest a general visual processing impairment as the deficit underlying pure alexia (letter-by-letter reading). It should be noted that in the patients of both Rapp and Caramazza and Farah and Wallace the deficit extends to non-verbal material, which was not investigated by Kay and Hanley.

An issue repeatedly discussed throughout the book is the 'attentional' versus 'representational' interpretation of neglect dyslexia. The relevant arguments echo the debate concerning visuo-spatial neglect in general. Caramazza and Hillis take the view that a representational account better captures the pattern of impairment of their patient. In two right brain-damaged patients with left neglect dyslexia, Riddoch, Humphreys, Cleton and Fery show that left cues may improve performance and conclude that a pathological rightward orientation of attention is a main underlying deficit. A definite adjudication between these two competing approaches is not an easy enterprise, and I wonder whether this is a really crucial problem of the interpretation of neglect. Most of the empirical findings reported in this book may be accommodated within either 'attentional' or 'representational' accounts (*see,* for instance, Rapp and Caramazza, p. 303). The fractionation of neglect dyslexia (and of visuo-spatial neglect) into a variety of specific deficits, however, may be readily accounted for in terms of an impairment at different levels of representation (see Caramazza and Hillis). Attentional hypotheses can also account for these phenomena, but at the cost of fractionating 'attention' into a number of different sub-components. Alternatively, a single attentional mechanism may serve all processing domains (representations), but any given individual domain may become disconnected from attention, thus producing selective deficits (Behrmann, Moscovitch and Mozer). It is apparent that such fractionated versions of the attentional hypothesis cannot be easily distinguished from the representational view.

According to the standard cognitive taxonomy of neuropsychological disorders of reading (*see* Riddoch's introduction), neglect dyslexia is classified as a 'peripheral' dyslexia since the impairment involves pre-lexical processes. This is also stressed in the book's title. The observation of lexical effects (in most patients, though not all, reading performance is better for words than for non-words) suggests, however, interactions with the lexical system. Behrmann *et al.* report studies in normal subjects and in brain-damaged patients. They show that the lexical/non-lexical role of left-sided distracting and unattended information affects lexical decision. Warrington suggests that in some patients with neglect dyslexia the deficit may be 'central' in that it involves word form units (see also Caramazza and Hillis). It seems clear from these few examples that the 'peripheral' versus 'central' nature of neglect dyslexia is an open issue, closely related to the ongoing debate regarding the fractionation of the disorder.

All the studies mentioned above involve single cases (a methodology widely used in cognitive neuropsychology) and are primarily concerned with a functional description of the patient's reading disorder, rather than with its neurological correlates. Sieroff's investigation of visual-verbal processing by left and right brain-damaged patients is the only group study in the book. The exception is more apparent than real, however, as Sieroff also makes a single-case analysis of the performance of his patients. While right brain damage yields the expected left extinction with double simultaneous stimulation, the pattern after left brain damage is more heterogeneous and does not lend itself to a straightforward interpretation.

The book provides a few, but not novel indications concerning the neural correlates of neglect and letter-by-letter dyslexias. Lesions in the right hemisphere, mainly posterior, produce a contralesional (left-sided) neglect disorder corresponding to left-right spatial coordinates (Riddoch *et al.*, Sieroff, Young *et al.*). Left-sided lesions, again mainly posterior, are associated with a less homogeneous neuropsychological pattern, including right-sided neglect at different levels in a multi-stage visual word recognition system (Caramazza and Hillis, Rapp and Caramazza, Warrington), selective impairment of initial letter identification (Patterson and Wilson) and letter-by-letter reading. The greater variety of deficits produced by left-sided lesions is likely to reflect the major involvement of the left hemisphere in reading-specific processes.

This series of papers on neglect and letter-by-letter dyslexias deserves to be read by students interested in the issue. Important neuropsychological problems are discussed and most papers are also excellent illustrative examples of the cognitive neuropsychological method. Efforts have been made to ensure appropriate cross-references among the different contributions. In reviewing this collection of papers as a book, I note an overlap between the Caramazza and Hillis and Rapp and Caramazza papers, where the visual word-recognition model is described twice and its schematic illustration is repeated (pp. 397 and 285). I found the page numbering of the book, which is that of the two original issues of the Journal, slightly confusing and it prevented an efficient use of the subject index. So, the book's first page is 369, the last 334. The book comprises a number of specific experimental papers, some of which (e.g. Caramazza and Hillis, Farah and Wallace) include literature reviews, though there are no review articles as such. This may limit its readership to neuropsychologists and psychologists specifically interested in and already familiar with the cognitive approach to the dyslexias. Neurologists concerned with the behavioural disorders produced by brain damage may also enjoy *Neglect and the Peripheral Dyslexias*, as long as they are aware that the neural correlates of these deficits are not the main focus of the book.

GIUSEPPE VALLAR

Fetal Neural Development and Adult Schizophrenia. Edited by Sarnoff A. Mednick, Tyrone D. Cannon, Christopher E. Barr and Melvin Lyon. *Longitudinal Perspectives in Schizophrenia Research*, 1991. Pp. 244. Cambridge: Cambridge University Press. Price £45.00

The way in which the likely origins of schizophrenia are conceptualized has changed fundamentally in the past 5 yrs. Psychosocial and political explanations for the disorder popular in the 1960s had already given way to an increased acceptance of organic explanations by the late 1970s. By the 1980s evidence in particular from one line of investigation, computerized brain imaging, was yielding a burgeoning body of evidence that subtle morphological brain abnormalities were present in a sizeable minority of schizophrenic patients. Given the nature of the disorder with its onset in early adult life, these abnormalities at first were seen to be evidence of a progressive neurodegenerative disorder. In the mid-1980s a reappraisal of this interpretation began and a consensus of opinion has emerged that these minor anomalies of brain structure are not after all progressive but are present in the earliest stages of the illness. By inference, they exist before the first recognizable stages of the disorder are manifest. At about the same time, concepts about how the immature brain developed were also changing. The notion became accepted that some forms of very early brain lesion could remain functionally silent until the surrounding nervous system gained sufficient organizational maturity to enable their recognizable expression. Static brain lesions could go undetected until normal neurological development had reached a stage advanced enough for problems to emerge. This idea has been grasped as the underlying tenet in the so-called neuro-developmental model of schizophrenia. This book is the first to mark the rise of this idea.

Dr Sarnoff Mednick, energetic as ever, has coordinated the production of this volume which in large part reports the proceedings of a meeting held in 1988 with the same title. Mednick is based at UCLA but made his reputation when involved in the 'Copenhagen High Risk Study' which followed through a cohort of children born in the 1960s to schizophrenic mothers. Out of this and other epidemiological databases in Denmark came several pioneering papers purporting to show the importance of early neurological factors and obstetric complications to the development of later schizophrenia, and the first paper to suggest the possible importance of prenatal influenza as a risk factor. A scientific audience, initially rather incredulous, has increasingly come to be persuaded by these findings as replications outside Denmark have followed.

The purpose of this volume is to explore the general hypothesis that neurological events at or before the time of birth can be relevant for the development of schizophrenia 20 yrs later or more. To do this Mednick has included sections which examine current knowledge about normal and abnormal developmental processes in the human brain and possible behavioural sequelae of such abnormal processes.

These basic science reviews provide much of the meat of the book. Two chapters are written by the developmental neuroanatomist Richard Nowakowski. The first is a 20 page review of the current knowledge about normal developmental processes in the early central nervous system. Some classical vertebrate embryology is followed by more recent insights into the complex cascade of delicate developmental events which become exponentially more complex as maturation proceeds. The first major organizational process is self proliferation in which baby neurons are generated in the ventricular neuroepithelium and then migrate to positions in the cortex along the radial tramlines provided by glial cells. This migration involves both passive displacement by the further emergence of new cells nearby as well as active locomotion by young neurons. The final stages in shaping the mature functioning cortex, axon proliferation and then elimination, are discussed and are taken further by E. G. Jones of the University of California in the following chapter. Here the development of the primate neocortex is reviewed in detail. In particular, evidence from animal lesion studies is described which points to the importance of early afferent activity in utero in ensuring the normal maturation and differentiation of cortex. Later, sensory activity is important in maintaining topographical organization in the cortex and the changes can be relatively swiftly translated into alterations in organization by the regulation of neurotransmitter gene expressions, particularly of GABA. The point is made that, as with the now familiar beat of a butterfly's wings causing, by virtue of chaos theory, an ice age a million years later, early perturbations in cellular development can have a profound later effect.

Richard Nowakowski in his second chapter reviews much of his own work which has gone towards identifying in the mouse, single gene mutations which can disturb cortical development. This is a relatively new area because single gene mutations in inbred strains of mice have until recently only been identifiable through disturbances in overt behaviour which usually means locomotor disturbances. For this reason much is known about cerebellar development but comparatively little was known about cerebral cortex since developmental abnormalities here do not usually affect overt behaviour. Nowakowski used the approach of comparing neuroanatomy rather than behaviour in different strains of inbred mice, concentrating on the hippocampus. From the point of view of this book, this was fortuitous since the hippocampus is fast acquiring the dubious reputation of being at the heart of almost every known psychiatric disorder from Alzheimer's disease to anxiety, with schizophrenia very much included in the list. Nowakowski describes the normal developmental anatomy of the hippocampus and goes on to outline a series of single gene mutations now identified in mice which often give rise to trails of ectopic cortical neurons leading away from the hippocampus, like a tram leaving patches of oil along the tramlines.

A subsequent chapter by three members of the department of embryology at the University of Copenhagen, presumably former colleagues of the editor, examines the possibility that some acquired or inherited defect in the developing blood brain barrier could lead to abnormalities in regions originally developed from the medial telencephalic wall: the hippocampus, dentate gyrus, parahippocampus and amygdala, and septal area. Although their argument remains highly speculative, these authors do provide an interesting review of the embryology of the blood brain barrier and how genetic and exogenous factors might produce localized damage. They note that various neurological diseases with a wide range of causative agents show a very uniform pattern of localized pathological changes in the brain. The hippocampal formation, in particular Ammon's horn, is targeted in a range of conditions from herpes simplex and rabies infections, lead intoxication, kuru and kernicterus. A further chapter by Melvin Lyon and Christopher Barr recapitulates the early chronology of brain development, but this time in the context of what is known about which developmental areas are most susceptible to neurological insult at what times. This is an interesting review, including, for example, the observation that the areas most vulnerable to disruption from hydrostatic changes in the ventricular fluid in the second trimester include the occipital horn of the lateral ventricles, the CA2 area of the hippocampus and the rostral corpus callosum. The chapter limits itself to reviewing the older neuropathological studies based on autopsy findings in neonates. It would have been strengthened if more recent studies using ultrasound and other brain-imaging techniques in infants and children at risk of obstetric brain injury had been included. In a companion chapter, the editors review the evidence for an association between the history of obstetric complications and adult schizophrenia. This is a difficult area to review since almost all the studies purporting to show a link have some significant methodological weaknesses. Most studies are at least partly retrospective and follow a case control design. The authors do not help their case by at no point defining obstetric complications and also including studies which were done in the 1960s in the USA looking at 'childhood psychosis', a defunct concept probably equivalent to infantile autism rather than anything to do with schizophrenia. It is likely that there is an increased rate of obstetric complications in the past history of adults with schizophrenia, although the exact cause and effect relationship can be debated. Mednick *et al.* take it as read that the evidence is conclusive and can only be interpreted in one causal direction. They do not mention the possibility that obstetric complications might be some epiphenomenon of an abnormally developing foetus which is later destined to become a schizophrenic adult.

Bernhard Bogerts of Dusseldorf is the acknowledged pioneer of the new wave of post-mortem studies in schizophrenia and he contributes an excellent review chapter examining critically the findings reported at autopsy and recent studies in schizophrenia. All such studies have been small but present the persuasive collective picture of morphological and histological abnormalities particularly in hippocampus, parahippocampal gyrus and amygdala. Many studies have noted the absence of gliosis thus supporting the notion that the structural anomalies are very early in origin. There is a good chapter by Breslin and Weinberger, the latter being one of the early elaborators of the neuro-developmental model of schizophrenia. In it structural brain imaging findings are reviewed in the context of the hypothesis that causative pathology occurs and arrests early in development and ontogenic pathology occurs and arrests early in development and ontogenic patterns of the maturing brain are related to the clinical cause. This model states that such brain pathology is present at the onset of the illness, is non-progressive and is relatively silent behaviourally in childhood before resulting in schizophrenic symptomatology in adult life. Breslin and Weinberger point out that medial temporal lobe lesions do not fit well with this model since primate studies indicate that such lesions are not silent in childhood, although these studies have in the main examined the effects of gross ablative lesions. The authors point to the dorsolateral prefrontal cortex as an area which does not reach functional maturity until adult life and speculate whether the critical lesion is not medial temporal pathology *per se* but its effect on ascending projections to prefrontal cortex.

Cannon and Mednick provide both the opening introductory chapter and the concluding chapter. The styles of these two chapters are curiously different. The opening introductory chapter is up-front and brash, putting forward a speculative so-called 'two hit' model of schizophrenia implicating a specific interaction between genes and obstetric complications. By contrast the closing chapter is a more considered evaluation of the evidence which pulls together in a critical way the findings reviewed in the book.

Taken as a whole this is a worthwhile book. Sections which are marred by over-generalization, speculation and hyperbole are more than compensated for by the excellent developmental neuroscience reviews and the reviews of neuro-developmental aspects of brain abnormality in schizophrenia. There are some areas which could usefully have been included: in particular, the increasing importance of molecular biology should have earned it a large section in the book. It is a useful source book for those involved in schizophrenia research and I suspect will remain so for some time to come, despite the fact that it arose out of a symposium held in 1988. It serves as an accessible landmark to what is proving to be a paradigm shift in schizophrenia, the proper understanding of which may well prove to be one of the final frontiers of medicine.

SHÔN LEWIS

Oxford Medical Databases: The London Neurogenetic Database. By M. Baraitser and R. M. Winter. 1992. Price £395.00 plus VAT

It is a sign of the times that *Brain* is now inviting reviews of computer software medical information systems for a section once devoted to discussion of the written word. Undoubtedly, one of the greatest advances in medicine over recent years has been the application and widespread use of computer technology and the invitation for review of this latest development acknowledges its growing importance.

Nowhere is the power of the silicon chip more welcome than the medical reference systems' help for the busy specialist who, faced with an ever-expanding medical science and accompanying information overload, can now access the literature quickly and easily and in a timely fashion to obtain answers to questions of direct relevance to patients. Computers in medicine are here to stay but for those who think that 'bytes' and 'RAM' might be painful afflictions to be avoided at all cost, fear not, the 'user-friendly' concept has arrived and computer literacy now has a short learning curve before competency is assured. No prior knowledge of computers is required to use the London Neurogenetics Database (LNDB), although experience with other IBM compatible software programs and a keyboard will make for greater speed of familiarity. I found that within a morning's use I had explored and used most of the facilities to my satisfaction, including customising the program to personal preference.

There is now a number of medical reference systems to which one can subscribe in order to keep abreast of developments and many readers will be familiar with the Compact Cambridge (CD-ROM) system available in many libraries. Unlike this system, however, the LNDB provides a comprehensive reference system in one database set which extends back over a century of medical publications, rather than requiring the user to search with disks by individual year, and is confined to neurological syndromes with a genetic basis, or which *may* have a genetic basis (e.g. adult onset motor neuron disease). A separate database, but one which can be used in conjunction with the LNDB, employing the same retrieval methods, is the London Dysmorphology Database. Most readers will be principally interested in the LNDB and I will confine discussion to this.

The LNDB has four main uses. First, it gives an abstract of core information relating to each of 2000 syndromes, much in the style that one might read in a textbook, with advice about traps for young players and cross-reference information to a differential diagnosis. Hence, if the user simply wishes to look up the recognized pertinent features of a known syndrome, they can be obtained together with a checklist of features, other syndrome names, the inheritance pattern and chromosomal location, if known. A list of the most relevant references is also provided on the basis of this search. After on-screen viewing, information can be directed to the printer or transferred to disk for inclusion in word processing documents and subsequent editing.

Secondly, having established the features (either clinical or inheritance pattern) of a patient with a hitherto unrecognized disorder, a range of syndromic possibilities combining these features can be derived and scanned to consider the alternatives, again with access to abstract information and references. Searches can be refined or expanded easily if the initial search provides too much or too little information. Subjective decisions have to be made about the most important features. The rarest syndromes are those which cause the most difficulty in clinical practice. The authors state in the accompanying handbook that the database is more a 'system for experts' rather than an 'expert system', to emphasize that the LNDB is not an alternative to taking an adequate family history and performing a physical examination.

Thirdly, the LNDB acts as a purely medical reference database which can be searched by author, year, journal, publisher and syndrome and, finally, it allows the user to store details on personal patients in records for future retrieval.

The features are menu-driven and self-explanatory, in typical fashion, with ample on-screen help. The short manual is also useful and includes a complete clinical features list which is also available on screen for selection and insertion in searches. The system has been 10 yrs in the making and is a further improvement on existing editions. In particular, this latest version now includes, amongst other improvements, synonymous titles in the main syndrome list; locate and search functions to allow searching on words and phrases appearing in synonymous titles; combinations of words and phrases when locating features; searching for syndrome and reference titles and limited options for controlling the printer output.

When putting the system to the test with a current neurogenetic clinical problem of dementia and stroke in young adults the system performed well and produced references of seemingly direct relevance, although a further search for a less well-defined syndrome of possible genetic basis, combining congenital heart disease, subtle dysmorphic features and an anterior spinal artery syndrome in a 19-yr-old male, was less helpful. The references are up to date, including, for example, the chromosomal localization of Kennedy's syndrome, and many other 1991 references.

Some syndromes, for example, Gerstmann-Straussler, do not have their own heading in the main list (included under 'spongiform encephalopathy'), so take some time to find. The references have been selected as there are limits to disk space, but one cannot complain with access to 15 000. Some references are included which do not have any genetics component; for example, discussions of disease aetiology. There is a number of spelling errors in abstracts and journal abbreviations, and more than one abbreviation may be used for the same journal (e.g. *Journal of Neurology, Neurosurgery, and Psychiatry*), neither of which are standardized to that currently employed in publications. This is disappointing if this tool is to be helpful in improving accuracy of communication. The features list is ordered in an anatomical fashion, rostral to caudal after 'neurology' features, but would be more useful if an option existed to reorder alphabetically. A facility which is not available, but which would be helpful, is the ability to export references into a personalized reference database system such as Reference Manager (Research Information Service inc.). For those less familiar with the terminology of the more obscure terms used for describing dysmorphic features, definitions would be helpful.

Taking more than 10 megabytes of hard disk space, it is suited to medium-large storage capacity personal computers and requires an IBM XT, AT or PS/2 microcomputer (or full compatibles), with a minimum of 640K RAM and DOS version 2.1 or higher. There is no facility for Macintosh users and clearly serious users will need to take advantage of the regular updates on a subscription basis.

The LNDB is an impressive, useful, comprehensive and powerful tool, easy and enjoyable to use. At an initial layout of £395 (excluding VAT) and an annual update subscription of £150, however, it is unlikely that neurologists without a special interest in genetics will feel the cost is justified, despite the huge amount of data provided and its intrinsic appeal. However, this facility certainly should be available in medical libraries and in regional neurology services, perhaps in conjunction with local departments of clinical genetics.

A. M. CHANCELLOR

ANNOUNCEMENTS

Course

The following course is being organized by the Institute of Psychiatry (University of London), the Maudsley Hospital and Bethlem Royal Hospital:

Women and Mental Health—Women and Community Care—a Multidisciplinary Approach', November 26–27, 1992.

For further information contact Mrs Lee Wilding, Conference Office, Institute of Psychiatry, De Crespigny Park, London SE5 8AF (Tel: 071 703 5411, ext. 3170; Fax: 071 703 5896).

Conferences organized by The New York Academy of Sciences

'The Role of Insulin-like Growth Factors in the Nervous System' at Crystal Gateway Marriott, Arlington, Virginia, USA, November 4–7, 1992

'Molecular Basis of Ion Channels and Receptors involved in Nerve Excitation, Synaptic Transmission and Muscle Contraction' at the Ibuka Memorial Hall, Waseda University, Tokyo, Japan, January 12–15, 1993.

'Slow Infections of the Central Nervous System: The Legacy of Dr Bjorn Sigurdsson' at Háskólabió Conference and Cultural Centre, Reykjavik, Iceland, June 2–5, 1993

For further information contact the Conference Department, The New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021, USA (Tel: 212 838-0230; Fax: 212 888-2894)

International Congress on Neurology and Neurosurgery at the Third International Symposium on Epilepsy

These two events will be held in Havana, Cuba, December 7–11, 1992 For further information contact Professor Otto Hernández Cossio, President of the Organizing Committee, Apartado 4248, Zona Postal 4, Ciudad de la Habana 10400 Cuba (Tel: 32-7825, Telex: 511609 palco cu; Fax. 22-8382 and 20-2350).

MRI Update 1993: MR Imaging of the Head, Spine and Musculoskeletal System

The eighth in a series, this continuing education course is being presented by the Medical College of Wisconsin and Continuing Medical Education, Inc. at the La Quinta Golf and Tennis Resort in La Quinta, California, USA, February 22–26, 1993. For information contact Marti Carter, CME, Inc., 11011 W. North Ave, Milwaukee, WI 53226, USA (Tel. 414 771-9520)

The Eighth Conference of the South East European Society for Neurology and Psychiatry

This conference will take place in Jerusalem, Israel, February 28–March 3, 1993. For information contact Professor S. Feldman, The VIII Conference of the South East European Society for Neurology and Psychiatry, c/o PO Box 50006, Tel Aviv 61500, Israel (Tel: 972 3 5174571; Fax: 972 3 655674).

The Fourth International Bethel-Cleveland-Epilepsy Symposium: Seizures and Syndromes

This symposium will be held in Bielefeld, Germany, March 11–14, 1993. For information contact Dr S Noachtar, Epilepsie-Zentrum Bethel, EEG Abteilung, Maraweg 21, 4800 Bielefeld 13, Germany (Tel: 05 21/1 44-36 99).

The Seventh Annual Magnetic Resonance Imaging Conference

This conference, organized by the Barrow Neurological Institute of St Joseph's Hospital and Medical Center, will be held at the Arizona Biltmore Resort Hotel, Phoenix, Arizona, USA, March 14–17, 1993. For information contact Maria Sodaro, R.N., B.S.N., Research and Education Coordinator, Radiologic Education Center, St Joseph's Hospital and Medical Center, 350 W. Thomas Road, Phoenix, AZ 85013, USA (Tel: 602 285-3956).

The International Congress on Advances in Brain Revascularization

This congress is scheduled to take place in Eilat, Israel, April 18–23, 1993. For details please contact the congress secretariat c/o Ortra Ltd, PO Box 50432, Tel Aviv 61500, Israel (Tel: 972-3-664825; Fax: 972-3-660952).

The Second International Conference on Stroke

This conference will take place in Geneva, Switzerland, May 12–15, 1993. For information contact N. M. Bornstein, MD, International Conference on Stroke, c/o Kuowi Travel Ltd, 7 Rue de Berne, CH-1211, Geneva 1, Switzerland (Tel: 41 22 732 0888, Fax: 41 22 731 5078).

The Ninth International Symposium of Brain Edema

This symposium will be held in Tokyo (Pacifico Yokohama), Japan, May 16–19, 1993 For information contact Umeo Ito, MD, Department of Neurosurgery, Musashino Red-Cross Hospital, 1-26-1, Kyonan-cho, Musashino-shi, Tokyo 18, Japan (Tel: 81-422-32 3111; Fax: 81-422-32 3525)

The Twentieth International Epilepsy Congress

This congress will be held in Oslo, Norway, July 3–8, 1993. Satellite symposia are being planned for the days preceding the Congress The deadline for submission of abstracts is December 1, 1992. To submit abstracts or obtain further information on the Congress, contact Svein I. Johannessen, Ph.D., Secretary-General, 20th IEC, The National Center for Epilepsy, N-1301 Sandvika, Norway (Tel 47-2-54 10 60; Fax: 47-2-54 53 21).

The Seventh World Congress on Pain

This congress, sponsored by the International Association for the Study of Pain, will be held in Paris, France, August 22–27, 1993 For information contact Louisa E. Jones, International Association for the Study of Pain, 900, NE 43rd Street, Suite 306, Seattle, WA 98105, USA (Tel 206-547-6409; Fax: 206-547-1703)

The Fourteenth Biennial Meeting of the International Society for Neurochemistry

This meeting will be held in Montpellier, France, August 22–28, 1993. Deadline for submission of abstracts is February 1, 1993. Those interested in organizing Colloquia or Round tables should address their request to Dr Jean de Vellis, Chairman of the ISN Programme Committee, University of California at Los Angeles, Mental Retardation Research Center, Neurobiochemistry Research Center, Neurobiochemistry Group, 760 Westwood Plaza, Rm 68-225 NPI, Los Angeles, CA 90024-1759, USA Other enquiries to Dr Max Récasens, Chairman of the ISN Local Organizing Committee, INSERM U 254, Laboratoire de Neurobiologie de l'Audition, Hôpital St Charles, 34059 Montpellier cedex 1, France (Tel· 33 67 33 65 15, Fax: 33 67 52 56 01).

The Thirteenth International Congress of EEG and Clinical Neurophysiology

This congress, organized by The International Federation of Clinical Neurophysiology, will be held in Vancouver, BC, Canada, August 29–September 4, 1993. For further information contact Information Secretariat, 645-375 Water Street, Vancouver, BC, Canada, V6B 5C6 (Tel 604-681-5226, Fax 604-681-2503).

The Second World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) Meeting

This meeting will be held in Los Angeles, California, USA, September 8–11, 1993 For information contact Dr Om P Sharma, Room 11-900, LAC/USC Medical Center, 1200 N State Street, Los Angeles, CA 90033, USA (Tel: 01-213-226-7923; Fax: 01-212-226-2738).

The Sixth Congress of the European College of Neuropsychopharmacology

This congress will take place in Budapest, Hungary, October 10–14, 1993. For information contact Peter Gaszner, Hùvosvòlgyi út 116, Budapest, H-1021, Hungary *or* Congress Bureau MOTESZ, Ms Krisztina Szigedi (Tel: 361 251-7999, 163-0037, 163-3899, Fax: 361 183-7918)

Volvo Award for CNS Injury Research, 1993 by the Neurotraumatology Committee of the World Federation of Neurosurgical Societies

In order to encourage research aimed at injury prevention analysis and mitigation of central nervous system injuries, the Volvo Company of Göteborg, Sweden has sponsored an award for 1993 of US$5000.

Papers entering the contest must contain **original** material, not previously submitted for publication. Multiple authors is acceptable The manuscripts, in the English language, should be full-length, including original illustration, in a form suitable for submission as an original paper (not postgraduate thesis) to a scientific journal. One original and five copies of each paper in full must reach the address below **not later than February 1, 1993**.

One of the authors should be prepared to come to Acapulco, Mexico, at his own expense, for the 10th International Congress on Neurological Surgery, October 17–22, 1993 to present the paper and to receive the award.

The board of referees will be chaired by Professor Daniel Stålhammar and will contain members chosen by the Neurotraumatology Committee of the World Federations of Neurosurgical Societies. Please direct all correspondence to Daniel Stålhammar, Division of Neurosurgery, Sahlgren Hospital, S-413 45 Göteborg, Sweden.

BIBLIOGRAPHIC REFERENCES should be limited to essential literature. They should be listed at the end of the paper in alphabetical order and not numbered. For a citation from a *journal*, the author's name in capital letters and the year of publication in brackets are followed by the title of the paper, the name of the journal *in full* and underlined for italicization, the volume number and the first and last pages of the journal. For multiple publications by the same author, those by the author alone are listed first and any with two or more co-authors listed subsequently in chronological order. The names of all authors must be given up to a maximum of six and any more should be indicated by *et al.* If there is more than one paper for a given year, these should be listed *a, b, c,* etc , after the year. For *books*, the author's name and year of publication in brackets are followed by the title of the book, underlined for italicization, place of publication, publisher's name and first and last page numbers For *chapters in books*, the author's name and year of publication in brackets is followed by the title of the chapter, the title of the book (underlined), preceded by 'In ', the name(s) of the editor(s), the place of publication, the name of the publishers and the first and last pages of the chapter

DEXTER DT, CARAYON, A, VIDAILHET M, RUBERG M, AGID F, AGID Y *et al* (1990) Decreased ferritin levels in brain in Parkinson's disease. *Journal of Neurochemistry,* **55,** 16–20

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TRAVEL GRANTS

The Guarantors of Brain are prepared to consider applications for part or all of the costs incurred by clinical and non-clinical neuroscientists, aged under 40 and based in the United Kingdom, wishing to visit laboratories or clinical departments at home or abroad. Awards of up to £2000 may be available.

Applications will be considered for attendance at scientific meetings which relate directly to the applicants' research interests. Only exceptionally will applications to attend larger international conferences be considered. The Guarantors are unlikely to meet all of the costs of these visits and encourage applicants to seek part of their expenses from other sources.

Four copies of each application must be submitted at least two months before the planned date of departure.

The following documents are required:

1. An abbreviated curriculum vitae with a list of publications.
2. An account of the purpose of the visit.
3. The names of two referees.
4. A letter of invitation from the Host Department.
5. A statement of the costs with details of related applications.
6. A list of previous awards given by the Guarantors of Brain.

The applications should be sent to Professor Richard Frackowiak, MRC Cyclotron Unit, Hammersmith Hospital, 150 Ducane Road, London W12 0HS, UK. (Tel 081 994 6945).

All successful applicants are expected to submit a short report of the visit on their return.

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